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**Acute Effects of Transdermal Nicotine on EEG and Mood
During Short-term Smoking Deprivation**

by

M.A. Bosman, B.Sc.(Hons.)

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

Master of Arts

Department of Psychology

**Carleton University
Ottawa, Ontario**

19 December 1995

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During Short-term Smoking Deprivation"

submitted by Melissa A. Bosman, B.Sc.(Hons.)
in partial fulfilment of the requirements for
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Abstract

Smoking has been repeatedly reported to elicit electrocortical effects which are psychostimulating in origin. Similar findings have been reported among dependent smokers, non-deprived smokers as well as in the non-smoker population. Although the majority of transdermal nicotine studies are clinical cessation trials, the transdermal patch has been shown to produce plasma levels of nicotine similar to smoking as well as mediate negative affective states believed to be related to smoking withdrawal. This suggests a similar effect on electrocortical arousal—as measured by EEG recording techniques—which, to date, has not been previously explored. The acute independent effects of transdermal nicotine patch administration on electrocortical arousal and self-reported mood changes and their relationship was studied. Sixteen male heavy smokers, screened according to inclusionary/exclusionary criteria, participated in this study. Participants were tested within a repeated measures randomized block design where dependent measures (EEG recording, Profile of Mood States Questionnaire) were sampled across two nicotine levels (placebo and 21 mg nicotine) at five separate time intervals (pre patch application and 1,2,3,4 hour post patch application). The results indicated that nicotine appears to reduce slow wave band (delta and theta) amplitude and increase alpha 2 and beta 2 amplitude. Conversely, placebo appears to increase slow wave amplitude while decreasing alpha 2 and beta 2 amplitude. Nicotine appears to primarily mediate affect related to vigilance (i.e. fatigue and vigor). The results of the present study appear to confirm the psychostimulant-like EEG profile reported by previous smoking-EEG studies.

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Introduction

Addiction vs. Functional Approach to Smoking Motivation:

Why do people smoke? The question of smoking motivation has been subject to an ongoing debate concerning the importance of pharmacological and psychological factors, dominated by two theoretical approaches which have been forwarded to account for the motivation to initiate and maintain the smoking habit. A review of the literature suggests smoking motivation may not be as straightforward as suggested by the addiction model of cigarette smoking. Evidence suggests that smoking motivation is multi-causal, suggesting a functional model as the basis of smoking motivation.

The addiction perspective contends that cigarette smoking results in pharmacological dependence and that nicotine is the primary basis of the dependence process (West, 1992). According to this model, smoking is considered a drug taking behaviour directed towards the self-administration of nicotine. In a report by The Royal Society of Canada (1989) drug addiction is defined as:

... a strongly established pattern of behaviour characterized by (1) the repeated self-administration of a drug in amounts which reliably produce reinforcing psychoactive effects, and (2) great difficulty in achieving voluntary long-term cessation of such use, even when the user is strongly motivated to stop.

Evidence that habitual nicotine use may, like heroin or alcohol, fulfill the criteria of a drug addiction disorder is well established. In cigarette

smoking, puff by puff inhalation of smoke delivers a succession of nicotine "bolus" to the lungs and directly to the arterial system resulting in rapid nicotine spikes with peak nicotine blood concentrations being reached by the last puff of a cigarette (Russell, 1976). This rapid nicotine rise and peak provide pharmacological reinforcement with each puff.

However, research focused on the pharmacological aspects of nicotine does not integrate reinforcement from psychological and behavioural factors. Due to the focus on pharmacological aspects of dependence, other dimensions of dependence have largely been ignored by addiction theory proponents. Dependence is fundamentally a learned phenomenon and is multidimensional in nature. Sensory and environmental cues can become conditioned reinforcers and pharmacological effects are no more than one class of reinforcer. There are several possible mechanisms of nicotine reward. Nicotine may be reinforcing because it produces pleasurable effects, it modulates alertness and arousal or response to stressors and it may also act by alleviating withdrawal symptoms. In addition, learned and associated cues add to smoking satisfaction, including lighting-up routines and environmental factors. As suggested by Russell (1990), sensory and environmental stimuli can become powerful conditioned reinforcers and can serve as cues for the conditioning of craving and other affect related withdrawal effects. However, such factors appear to lose their motivational power without the reinforcing effect of nicotine (Ashton and Golding, 1989).

The functional approach regards smoking as a person's rationale choice to use smoke inhaled nicotine to control his or her psychological state, i.e. as a coping strategy for everyday problems, and it rejects the

widely accepted addictive habit theory of smoking motivation (Warburton, 1987). Proponents of this approach view smoking as the purposive outcome of the interaction of the person and the situation. As argued by Warburton (1987), depending on the situation, smokers continually adjust their smoking behaviour and their resultant nicotine dosing, thereby modulating mood and performance levels to meet the specific situational demands. Within this functional/arousal modulation model, deprivation of cigarettes results in the loss of a pharmacological tool and the appearance of abstinence symptoms due to the perceived loss of an effective psychopharmacological agent, manifested by disturbances in arousal and mood and reduced efficiency in information processing as indexed by decrements in performance on tasks requiring sustained attention and effort.

The functional view of smoking motivation stresses the usefulness of smoking in the improvement of psychological well being, arousal control, the reduction of stress and performance efficiency (Stepney, 1979). Smokers frequently self-report reductions in negative affect (Gilbert, 1979) following smoking and many studies have reported increases in performance in terms of speed and accuracy indices in information processing tasks (Wesnes and Warburton, 1983). Smoking affects all of the major functional systems governing human behaviour including those for reward/punishment, arousal, learning and memory (Ashton and Golding, 1989). As suggested by Henningfield (1984), the anxiolytic and anorectant (performance and mood regulation) effects of smoking are potentially therapeutic. Given the functional benefits of smoking, it is not surprising that individuals with high degrees of psychopathology have been found to

be likely to take up the smoking habit to self-medicate negative affect (Seltzer and Oechsli, 1985). In a literature review of the paradoxical tranquilizing and emotion reducing effects of nicotine in humans and animals, Gilbert (1979) concluded that the mechanisms by which nicotine modulates emotional responsivity are influenced by a multiplicity of variables including behavioural activity, central arousal, affect type, time since administration of nicotine and dose of its administration.

Non-pharmacological aspects of smoking include taste, sensory responses in the throat and upper airway, behavioural manipulation of the cigarette as well as social aspects of cigarette smoking (Robinson and Pritchard, 1992). Experimental evidence demonstrates the importance of sensory factors in smoking motivation as anesthetization of the mouth, throat, and upper airway was found to significantly reduce self-reported desire to smoke in a group of regular smokers (Rose et al., 1985). In a subsequent study, Rose, Behm and Levin (1992) administered an aerosol containing cigarette smoke constituents (low in nicotine but high in sensory impact). Subjects regulated their smoking behaviour to equate sensory intensity rather than nicotine intake, highlighting the importance of sensory cues in the regulation of smoke intake and modulation of craving.

Nicotine is self-administered by humans in the form of tobacco smoke and is considered to be the primary factor responsible for substance seeking behaviour. However, until the 1980's evidence indicated that animals will self-administer nicotine under some circumstances (Goldberg et al., 1981) but it appeared nicotine reinforcement was not demonstrated as readily as suggested by addiction theory proponents. Nicotine reinforcement appeared to be weak - with a longer acquisition period and

much lower response rates - in comparison with that produced by other substances including psychomotor stimulants and opiates (Collins et al., 1984). This difficulty in establishing nicotine self-administration has been interpreted a low 'addiction liability' in comparison with cocaine and heroine (Bozarth, 1990). Drug addiction appeared to require more than simple activation of the ventral tegmental reward system, i.e. neuroadaptive changes in this system may be involved (Bozarth, 1990). However, more recently Corrigan (1991) suggests that nicotine can serve as a strongly reinforcing drug in rodents when made available on a 'limited-access' schedule.

In addition, as reviewed by O'Connor (1989), human titration studies highlight the fact that the association between nicotine content and smoking behaviour is more complex than the addiction theory suggests. It is possible that variations in smoking style are attempts to manipulate the amount of nicotine inhaled (i.e. titration strategies). However, evidence suggests that not all smokers smoke principally to obtain nicotine as some smokers will not compensate for changes in nicotine concentration (Rose, Behm and Levin, 1992) and smokers who smoke mild cigarettes may not do so for nicotine content (Domino, 1973).

In summary, the addiction theory which maintains smokers gain reward from relief of nicotine withdrawal symptoms (i.e. negative reinforcement) does not account for all of the observations concerning smoking. In contrast, the functional psychological tool perspective incorporates the arousal modulation theory that smokers self-regulate nicotine intake to control arousal level (Ashton and Golding, 1989) and accounts for individual differences among smokers who use cigarettes as a

'tool' which provides needed psychological benefits including increased mental alertness, anxiety reduction and stress coping mechanisms (Warburton, 1987). Stepney (1979) pointed out the primary difference between the two approaches:

The two approaches are different to the extent that the addiction view holds that smoking is rewarding because it staves off the consequences of nicotine deprivation whilst the psychological tool view holds that smoking continues to be rewarding, in the appropriate context, in its own right.

West and Schneider (1987) have argued that cigarette smoking can best be understood in terms of an interaction of the two theoretical approaches. It is reasonable to assume that individual differences and environmental factors play an integral role in smoking behaviour. It appears that nicotine maintains the smoking habit and social, psychological and individual state factors act as modulators of smoking behaviour.

Nicotine, Arousal, Mood and EEG

Cigarette smoking has multidimensional effects including behavioural, psychological and physiological. It has been well documented that nicotine is the dominant psychoactive agent in tobacco smoke and has a direct and powerful effect on the central nervous system. However, attempts to demonstrate the equivalence of the effects of smoking and nicotine have been problematic. Nicotine appears to exert its effects on brain systems mediating arousal and affect as well as sensory/motor

functioning and may indirectly stimulate reward systems, ultimately providing motivation for continued smoking.

Electroencephalographic (EEG) analysis has been applied historically as an index of arousal or alertness (Berger, 1929) providing information on brain state and physiological effects of substances including nicotine and as such is a valuable tool in smoking research. The EEG consists of an oscillating signal varying in amplitude (μ V), frequency (Hz) and phase. Quantitative analysis of the EEG signal by such methods as Fast Fourier Transform (FFT) typically computes amplitude/power in four characteristic frequency bands: delta (below 4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (above 13 Hz). Berger (1929) discovered the alpha rhythm and demonstrated its sensitivity to events influencing arousal, noticing that the alpha rhythm was abundant in resting conditions and was reduced with mental effort or exposure to unpleasant stimuli. EEG patterns appear to vary along the behavioral-arousal continuum with EEG shifting from fast desynchronized activity during emotional excitement to rhythmic synchrony (alpha rhythm) during quiet relaxed wakefulness and to a progressively slower rate of synchrony in the successive stages of sleep (Lindsley, 1952). Smoking induced shifts in EEG frequency towards greater activation have been reported at widely differing doses of nicotine (Gilbert, 1979).

Smoking induced reports of reduced negative affect and behaviour are common but unexpected considering nicotine induced increases in arousal of the autonomic (ANS) and central nervous system (CNS). The ascending reticular activating system (ARAS) has been reported to be the underlying neurophysiological system mediating arousal. This system

consists of a complex mixture of nuclei and fibre tracts which stretch from the diencephalon through to the hindbrain (Kolb and Whishaw, 1990). Through the influence of experimental findings, the function of this system has been described as maintaining general arousal/alertness or consciousness. In an early investigation, Moruzzi and Magoun (1949) electrically stimulated the brainstem of anaesthetized cats and concomitantly recorded activity directly from the surface of the cortex. The resting EEG, which consisted of large-amplitude slow waves characteristic of sleep, was immediately replaced by a desynchronized low amplitude pattern typical of wakefulness following ARAS stimulation (Kolb and Whishaw, 1990).

Acetylcholine has been implicated in the neurochemical effects of nicotine on the brain. Knapp and Domino (1962) investigated the action of nicotine on the ascending reticular activating system in four species of animals. Nicotine, at an EEG activation dose of 10-20 µg/kg, resulted in blood levels of nicotine commonly achieved in human habitual smokers and produced EEG activation (low voltage, fast frequency rhythm) responses with midpontine but not prepontine transections in all four species studied. The authors postulated a ponto-mesencephalic site of action for the EEG activation effect of nicotine and tentatively speculated that nicotine produced EEG activation by releasing acetylcholine in the CNS. Subsequent work with 'smoking' doses of nicotine (2 µg/kg every 30 sec.) reported that nicotine did produce activation of cortical cells and release of acetylcholine at the cortex in cats (Armitage, et al., 1969). Exposure to higher concentrations (single dose 80 µg/kg) have been shown to decrease electrocortical arousal and decrease cortical output of acetylcholine

(Armitage et al., 1969), interpreted as demonstrating a biphasic action of nicotine.

The molecular similarity of nicotine to the endogenous neurotransmitter acetylcholine (ACH) enables nicotine to combine with ACH receptors to mimic the nicotinic action of ACH - initial excitatory action possibly followed by an inhibitory one (Mangan and Golding, 1984). The widely distributed ACH receptors in autonomic ganglia, neuromuscular junctions and subcortical structures and the resemblance of nicotine to ACH means that nicotine may have effects, both directly and indirectly on cholinergic systems (Armitage, 1979). In addition to acetylcholine, other neurotransmitters have been implicated in the neurochemical effects of nicotine on the brain. Evidence suggests that nicotine may stimulate dopamine transmission in the limbic system. Nicotine (as well as amphetamine and other drugs with abuse potential) have been shown to increase extracellular dopamine concentrations in both the nucleus accumbens septi (a limbic area) and the dorsal caudate nucleus (a subcortical motor area) (Di Chiara and Imperato, 1988). In addition to its effect on acetylcholine and the catecholamines, nicotine stimulates the release of an endogenous opiate as well as numerous other hormones such as vasopressin, growth hormone, prolactin and beta-endorphin, which are believed to have effects on behaviour and subjective state (Pomerleau and Pomerleau, 1984). In summary, nicotine action at cholinergic synapses can affect almost every body system (including behavioral, somatic and reward systems) either directly or indirectly via release of neuromodulators and neurotransmitters, initiating a cascade of activity.

The biphasic action of nicotine (i.e. stimulating and then blocking cholinergic synapses in arousal systems) has been documented using both subjective and objective indicators (Ashton, Millman et al., 1973; Domino, 1979; Gilbert, 1979). Smoking can produce changes in cortical activity which implies both an arousing and calming effect of nicotine. Recently, Norton, Brown and Howard (1992) examined the effects of smoking on the balance of activity of the cerebral hemispheres of smokers (i.e. lateralization of alpha and beta power) and found biphasic-dose dependent effects. Low doses of nicotine (i.e. low nicotine yield cigarettes) increased left hemisphere activity, as reflected by alpha suppression, in a dose related manner. Higher doses (> 1.1 mg) were associated with greater shifts towards right hemisphere activation as indicated by beta and delta lateralization and greater decreases in subjective arousal. These results support the hypothesis that the stimulant activation of lower doses of nicotine involves activation of the left hemisphere while the sedative effect of higher doses involves increased activation of the right hemisphere believed to mediate emotion (Norton, Brown and Howard, 1992).

The biphasic arousal model suggests that different types of smoker strategy might reflect the desire of the smoker to increase or decrease arousal and is based on an early theory of personality (Eysenck, 1973) which viewed behavioral differences of introverts and extraverts to be a reflection of high and low cortical arousal levels, respectively. It has been shown in animals that the pre-drug, baseline state of an organism can modify the uptake, metabolism and neurochemical effects of nicotine (Essman, 1973) as well as nicotine-induced behavioral effects (Domino, 1973). The arousal state dependent effects of nicotine on EEG supports

evidence that nicotine reduces cortical activation when activation is high but stimulates activation when cortical activation is low (Eysenck, 1973). This is consistent across other drugs including amphetamine. Kelleher et al. (1968) showed amphetamine produced depression of high baseline rates of operant responding and elevation of low baseline rates. Evidence from contingent negative variation (CNV) indices of cortical arousal, a slow negative potential appearing between the warning and imperative stimulus of forward reaction time paradigm suggest that smoking can be either arousing or sedating depending on the nature of the stimulus and the personality characteristics of the individual. Nicotine (12.5 to 800 µg range) has been shown to produce dose-related biphasic effects on CNV so that while smaller doses produced an increase in CNV magnitude (stimulant effect), larger doses produced a decrease of the CNV (depressant effect) (Ashton et al., 1980).

Pomerleau and Pomerleau (1984) reviewed findings of the neuroregulatory effects of nicotine and suggested a unified hypothesis to explain the persistence of smoking behaviour. The authors confirmed early reports of nicotine's biphasic dose-dependent effects (Domino, 1967). Pomerleau and Pomerleau stated it is possible that low doses of nicotine from smoking can enhance arousal by stimulating cholinergic and catecholaminergic activity (Wesnes and Warburton, 1983) and suggested in higher doses this initial phase of activation may be followed by sedation or relaxation resulting from cholinergic blockade. It is possible that nicotine may produce direct physiological and biochemical changes which, in addition to relieving negative affect, enhance performance and/or alleviate anxiety. Evidence suggests that smokers will adjust nicotine intake to

selectively enhance one component of the biphasic response or the other. As previously reviewed, the behavioral effects of endogenous neuroregulators occur independently of smoking or nicotine administration, but because nicotine can alter the bioavailability of these substances, nicotine may be used by smokers to "fine tune the body's normal adaptive mechanisms" (Pomerleau and Pomerleau, 1984).

For example, smoking reduces negative affect (Gilbert and Welser, 1989). The involvement of mood regulation in smoking motivation is supported by independent studies of EEG asymmetry which indicate that certain regions of the cerebral hemispheres are lateralized for the processing of affective stimuli. The right hemisphere appears to be more influenced than the left hemisphere (Gilbert, 1987; Gilbert, 1989) and during stress, increased alpha power has been reported in the right hemisphere relative to the left hemisphere subsequent to smoking a normal nicotine delivery cigarette (Gilbert, 1989). In no stress situations, following smoking, a greater activating effect (reduced alpha and theta band power) has been found in the right hemisphere compared to the left (Gilbert, 1987). Differential cortical activation asymmetries occur in response to positive and negative affective stimuli and have been reported predominantly in the frontal region with greater left hemisphere frontal activation during positive affect compared to negative affect and vice versa (Davidson et al., 1979). Frontal asymmetry for positive and negative affect has been shown to be present in human infants during the first year of life (Davidson and Fox, 1982). However, some studies have found no evidence of hemispheric asymmetry patterns of frontal activation. Meyers

and Smith (1986) reported bilateral activation of frontal lobes in response to positive affective stimuli with no evidence of hemispheric asymmetry.

Disorders of emotion/affect have been shown to display patterns of electrophysiological asymmetries which are different from normals. A large body of evidence suggests that depressed individuals differ from non depressed in measures of alpha power asymmetry in anterior and posterior scalp regions (Davidson, Schaffer and Sharon, 1985; Henriques and Davidson, 1988). Most consistently, depressed subjects have been shown to differ from controls in frontal activation asymmetry. Depressives have been found to show less left sided frontal activation (i.e. more left frontal alpha power) and less right posterior activation compared to controls. These effects have been shown to occur separately (Tucker et al., 1981) or together (Davidson et al., 1987).

However, a large number of EEG studies concerning cerebral lateralization of emotion have used single site recordings (typically frontal) and have been restricted to the alpha frequency band. Investigations of parietal recording sites (Smith et al., 1985; Gilbert et al., 1989) have also found significant hemispheric effects. Greater alpha suppression and therefore greater activation at the left parietal site was seen during emotional stimulation. Collet and Duclaux (1987) examined EEG lateralization of positive and negative affective stimuli using 16 electrode sites and failed to replicate the results of previous studies. No frontal alpha lateralization was found but a tendency towards centro-parietal lateralization was found. The laterality ratio score for positive affective stimuli was significantly higher on the right for alpha activity in centro-parietal areas.

Many multi-site studies point to the predominant role of the right hemisphere in the processing and expression of emotion. Significant main effects of hemisphere have been found in alpha and beta frequencies for parietal and temporal areas and delta/theta frequencies for temporal and frontal areas with greater power in the right hemisphere in all cases (Cole and Ray, 1985). Similarly, Ehrlichman and Weiner (1980) reported greater right hemisphere activation (tempoparietal region) during positive emotional tasks in both 2-12 Hz and 8-12 Hz bandwidths. Tucker et al. (1981) included frontal sites in a multi site recording study and replicated earlier single site findings implicating anterior regions of the brain in emotional arousal - greater alpha peak power activity in right frontal region.

As indicated by previous studies, mood related changes in cortical activation do not appear to be homogeneous across brain regions. This is not surprising considering arousal and emotionality have been traditionally viewed as related processes. Given nicotine may directly or indirectly stimulate mood regulating centres in the brain (i.e. limbic system), nicotine should affect the same regions found to be implicated in mood regulation. Evidence suggests (Gilbert et al., 1989) that nicotine acts to inhibit subjective experience of negative affect by reducing right hemisphere and/or by increasing left hemisphere based activation. Both left and right alpha power were significantly greater (i.e. less activation) prior to negative affective stimuli and were significantly less during stimuli presentation. High nicotine yield cigarettes during affective stimuli were found to reduce right hemisphere activation and the ratio of left hemisphere parietal activation to right hemisphere activation was enhanced. Therefore

the anxiolytic effects of nicotine may be mediated primarily by the right hemisphere.

In summary, as suggested by Gilbert and Welser (1989), nicotine appears to influence emotional processes by "priming neutral and/or positive affect-related processing and/or by inhibiting processing contributing to negative affect." Experimental evidence suggests this may be accomplished by nicotine's tendency to decrease activation of the right hemisphere relative to the left hemisphere (Gilbert, 1989). In addition, consistent with the functional perspective, evidence suggests the affect modulation induced by nicotine may be caused by nicotine's dose-response posterior to anterior spread of cortical activation. As suggested by Knott (1989b), smokers who smoke high yield cigarettes may do so to enhance psychological states/processes associated with frontal brain regions, whereas low yield smokers may seek to augment states/processes associated with posterior brain regions. Moreover, as suggested by Pomerleau and Pomerleau (1984), smokers exert 'finger-tip' control over smoking intensity to modulate the body's adaptive mechanisms. Furthermore, it is not surprising that individuals characterized by high degrees of psychopathology are likely to take up the smoking habit to self medicate negative affect (Seltzer and Oechsli, 1985). In fact, psychotropic drugs employed for the treatment of mood disorders also result in spreading of EEG activation from posterior to fronto-central regions (Coppola and Herrmann, 1987).

Quantitatively analyzed EEG has been utilized in acute test dose paradigms to establish the impact of CNS compounds in normal volunteer subjects. In general, it has been established that substances exerting

measurable EEG changes are associated with psychoactive/behavioral effects, while substances that do not alter the EEG do not appear to exert any psychoactive/behavioral effects (Herrmann, 1982). Furthermore, substances with similar behavioral/therapeutic effects (e.g. all psychostimulants) have, in general, been found to produce similar EEG test-dose profiles while substances with dissimilar behavioral/therapeutic effects (e.g. psychostimulants vs. neuroleptics) tend to produce distinctly different EEG test-dose profiles (Saletu, 1987). In general, EEG literature suggests that psychostimulant profiles induced by d-amphetamine and methamphetamine are characterized by an increase in total power, reductions in slow wave power, increases in alpha wave and slow beta (13-20 Hz) power and non-significant changes in fast beta wave power over 20 Hz. The anxiolytic sedative profile in contrast, is characterized by a decrease in total power and in alpha power and by increases in beta band power (Saletu, 1987). The majority of acute smoking/nicotine-EEG profile studies have been couched within arousal theory and as such, have been viewed as a cornerstone of functional/psychological tool models of smoking motivation. Evidence of electrocortical arousal shifts by smoking/nicotine is believed to indirectly reflect activation of motivationally significant brain reward systems (Church, 1989).

Smoking, Nicotine and Human EEG

Early studies investigating the differences in EEG activity between smokers and nonsmokers found that spontaneous EEG recordings of heavy smoker subjects are distinguishable from non-smokers. Brown (1968)

found that relative to non-smokers, nondeprived heavy smokers possessed EEGs characterized by some of the features usually associated with cortical arousal. Other studies investigating the differences in EEG activity between smokers and nonsmokers (Knott and Venables 1977, Knott, 1979) found that the EEG of nonsmokers as indexed by the peak alpha frequency (PAF) index (the alpha frequency containing the most power) was more activated (ie. was faster at 10 Hz) than that of cigarette deprived (overnight) smokers who exhibited a resting PAF of 9.3 Hz. This difference between nonsmokers and deprived smokers was not observed when comparing nonsmokers with nondeprived smokers and differences between nonsmokers and deprived smokers were immediately eliminated once the deprived smokers had smoked two cigarettes, as alpha frequency was found to increase to a level comparable to that seen in non-smokers.

EEG measurement has also been employed to examine the effects of short term smoking deprivation. Itil et al. (1971) examined the effects of smoking withdrawal on quantitatively analyzed EEG. After twenty four hours of deprivation, sleep like patterns and slower rhythms increased and were reversed by the smoking of three cigarettes. In general, literature suggests that smoking deprivation is accompanied by EEG signs of central nervous system sedation (Herning, Jones and Bachman, 1983). In contrast, smoking has been consistently followed by signs of EEG activation in deprived smokers (Knott and Venables, 1977). Similar arousing effects have been found with nicotine chewing gum in deprived smokers (Pickworth, Herning and Henningfield, 1986). The bulk of evidence favours the theory that nicotine is the pharmacological variable which accounts for shifts in cortical arousal during smoking.

Studies have also examined the role of individual differences on EEG in smoker vs. nonsmoker comparisons or between smoking deprived and nondeprived conditions. For example, Cinciripini's (1986) investigation examined the EEG effects of smoking in relation to coronary and non-coronary prone personality traits. Although both groups revealed clear EEG signs of behavioral arousal (i.e. alpha suppression) upon smoking after a four hour period of deprivation, the groups exhibited different patterns of change and different patterns of recovery, indicating the importance of personality traits (i.e. individual state factors) in mediating the effects of smoking.

In summary, despite differences in experimental design and recording methodology, early experimental studies, up to the late 1980's have yielded fairly consistent results: in resting, non task conditions, smoking suppresses activity in the lower frequency delta, theta and total alpha bands, raises the dominant alpha frequency and increases amplitude/power in the higher frequency beta 1 and beta 2 bands (Knott and Venables, 1977; Herning et al., 1983; Cinciripini, 1986). This pattern of change, switching from lower to higher frequency activity, is assumed to be characteristic of cortical activation. Similar power spectral effects have been noted following intravenous nicotine administration in humans. Lukas and Jasinski (1983) reported the administration of intravenous nicotine caused a dose related decrease in total EEG power due to a 50% reduction in alpha power. Several recent studies have reported slightly different acute smoking-related EEG profiles with total alpha being augmented, not reduced, with the smoking of one medium or low -

nicotine/tar yield cigarettes (Knott, 1988, 1989b). As previous studies differed from these latter two reports in using novel cigarettes (and not the smoker's regular cigarette), it has been suggested that increased alpha may reflect a psychostimulant effect (seen also with amphetamines) that the smoker is seeking or it may reflect the smoker's 'liking' of his/her daily, regular cigarette (Knott, 1990).

Studies employing multi-site EEG recordings for the examination of scalp electrical topography are consistent with single site EEG reports indicating a power shift to higher alpha/beta frequencies after nicotine intake. Using topographic EEG techniques to better understand the effects of tobacco smoking on different brain systems, Knott (1989b) determined a dose response effect of cigarette smoking. Smoking single cigarettes of increasing the nicotine yield resulted in a progressive posterior to anterior spreading of EEG total alpha power and a concomitant decrease in theta power. Domino, Riskalla et al. (1992) conducted a study to determine the effects of tobacco smoking on the topographic EEG of twelve hour-deprived heavy smokers. Tobacco smoking of high nicotine yield cigarettes caused a reduction in power in low alpha (alpha 1) frequencies and an increase in high alpha (alpha 2) frequencies, findings which were dominant in the occipital, parietal and frontal regions. Furthermore, Pritchard (1991) examined the effects of cigarette smoking on the EEG of smokers during both task and non-task conditions. In light inhaling smokers, smoking attenuated EEG activity in delta, theta and alpha frequency bands and facilitated behavioral performance. In deep inhaling smokers, smoking produced an increase in beta 2 amplitude, an EEG effect which was interpreted as being similar to the beta augmenting effects of anxiolytics.

These findings were argued as support of the functional perspective of smoking motivation, with light inhaling smokers smoking for purposes of mental activation and performance enhancement while heavy smokers employ smoking primarily as a means of anxiety reduction.

An important distinction to be made, as pointed out by Domino, Riskalla et al. (1992) is that by grouping the alpha frequencies into one bandwidth spanning 8-13 Hz, a decrease in amplitude of lower alpha (alpha 1) frequencies may mask an increase in the amplitude of higher alpha (alpha 2) frequencies. Therefore important shifts within alpha bandwidths can be missed by grouping frequencies into broader bandwidths. This may have been the case in earlier smoking/EEG studies where smoking-induced alpha reductions were the general trend in EEG studies. However some investigations have reported a shift to higher alpha frequencies after nicotine intake (Knott, 1988; Golding, 1988). As previously reviewed, Domino, Riskalla et al. (1992) provided additional evidence that tobacco smoking induces a state of wakefulness that results in enhanced alpha EEG activity with a shift from lower (alpha 1) to higher (alpha 2) frequencies.

If nicotine is the smoking component which accounts for shifts in cortical arousal, similar patterns of cortical arousal should be obtained across different mediums of nicotine administration. Nicotine in the form of smoked tobacco has, in general, been shown to increase EEG alpha frequency, decrease alpha 1 and theta power and increase both alpha 2 and beta power in the smoking deprived smoker (Herning, Jones and Bachman, 1983). Similarly, evidence suggests that nicotine gum shares somewhat similar, but limited, EEG stimulant profile effects like those of inhaled tobacco smoke, as both alpha peak increments and theta power

reductions have been reported (Pickworth, Herning and Henningfield, 1986). As previously discussed, these findings suggest that peak alpha frequency and theta power changes induced by smoking may reflect the true pharmacological effect of nicotine, whereas additional EEG changes may be related to non-pharmacological variables (Knott, 1990).

Smoking Cessation, Arousal Reduction and Nicotine Replacement

It has been reported that approximately 80 percent of smokers develop a withdrawal syndrome upon the cessation of smoking (Benowitz, 1988). Schiffman (1979), in a detailed description of the syndrome, reported that subjectively reported changes in arousal and mood are accompanied by objective changes in physiology and performance. Reports of decreased arousal have been supported by EEG studies indicating a decrease in peak alpha frequency and increases in low frequency activity following twenty-four hours of smoking deprivation - followed by reversal of neurophysiological changes within minutes of resumption of smoking (Ulett and Itil, 1969; Itil and Ulett, 1971).

Although the exact time of onset of cessation related symptoms is unknown, in many heavy cigarette smokers cessation related changes in mood and performance can be detected within two hours of last tobacco use (DSMIII-R, 1987). Most self-reported symptoms of withdrawal reach maximal intensity 24 to 48 hours after cessation and gradually diminish in intensity over a period of two weeks whereas some symptoms (i.e. the desire to smoke) may persist for months or years after cessation (Benowitz, 1988). As described by Schiffman (1979), the most common and clinically most important symptom is craving for tobacco.

Hatsukami, Hughes et al. (1984) provided convincing evidence that cigarette smoking abstinence is associated with a range of subjective, behavioral and physiological changes including: decreased heart rate, increased caloric intake, weight gain, increased craving for tobacco, confusion, depression/dejection, sleep disturbance and poor concentration (Hatsukami, Hughes et al., 1984). In this study changes in functioning occurred during cigarette deprivation, returned to pre-deprivation levels upon the resumption of smoking and re-appeared during a subsequent deprivation period.

The tobacco withdrawal syndrome has since been recognized by the American Psychiatric Association in the Diagnostic and Statistics Manual of Mental Disorders (DSM III-R, 1987). Clinical criteria for the diagnosis of a tobacco withdrawal syndrome (DSMIII-R, 1987) include: a) daily use of nicotine for at least several weeks and b) abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 hours by at least four of the following - craving for cigarettes; irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain. According to the DSMIII-R, additional associated features of smoking abstinence include increased slow rhythms on an EEG, decreased catecholamines, decreased metabolic rate, tremor, increased coughing, REM change, G.I. disturbance, headaches, insomnia, and impairment on tasks requiring vigilance. Although presently there is no universal consensus on a classification system of withdrawal, the DSMIII-R criteria are thought to provide the best scheme to date (Jarvik and Hatsukami, 1989).

Hughes and Hatsukami (1986) tested the validity of the signs and symptoms of tobacco withdrawal as defined by DSMIII by examining the relationship between both subject and observer-rated measures of tobacco withdrawal symptoms (as outlined in DSM III criteria) and blood nicotine levels in smokers. As found in earlier studies (Pomperleau, Fertig and Shanahan, 1983; Hatsukami, Hughes and Pickens, 1985a) smokers with higher nicotine/cotinine levels and change in nicotine level from pre- to post- cigarette reported greater craving during abstinence (overnight and four day deprivation periods respectively) than smokers with low nicotine/cotinine levels.

It is important to consider that although nicotine - in the form of cigarettes- may alleviate nicotine withdrawal symptoms, it should not be assumed that nicotine's effects on negative affect are simply a function of the elimination of such symptoms. As reviewed earlier, nicotine action at cholinergic synapses can affect many bodily systems either directly or indirectly via release of neuromodulators and neurotransmitters (Armitage, 1979). In other words, the tranquilizing/mood enhancing effects of nicotine may be independent of withdrawal relief. Evidence that quitting smoking is often associated with increased negative affect has been well documented (Gilbert and Welser, 1989; Gilbert et al., 1989). However, as suggested by Gilbert and Welser (1989), such symptoms would be expected whether nicotine relieves withdrawal symptoms or has direct negative-affect reducing properties similar to those of psychotropic compounds. In addition, the symptom of craving is common to reports of abstinence syndromes of many dependence producing drugs. Craving intensity appears to be directly related to the degree to which the drug activates

reward systems in the brain (Ashton and Golding, 1989). Evidence suggests that an opioid deficiency may underlie craving, unfortunately this has not been explored in tobacco abstinence. However, Pomerleau et al. (1987) found a trend towards reduced craving following acute exercise which elevated plasma beta-endorphin levels. Therefore, although the majority of nicotine replacement smoking cessation studies describe nicotine's role in alleviating negative affect associated with withdrawal (i.e. a classical psychopharmacological paradigm), nicotine has inherent anxiolytic and anorectant effects (Henningfield, 1984).

The relation between blood plasma nicotine levels and craving is supported by studies examining the withdrawal response to smoking cessation. In an early study Shiffman and Jarvik (1976) and later Cummings et al. (1985) reported the presence of a fairly consistent reduction in experienced withdrawal across days of cigarette abstinence. In addition, heavy smokers (> 20 cigarettes/day) tended to report more withdrawal symptoms than light (< 20 cigarettes/day) smokers. However, Gunn (1986), in a discussion of self report measures of withdrawal and craving after quitting 'cold turkey' in cessation clinics, criticized this claim of a clear correlation between amount smoked prior to cessation (i.e. plasma nicotine) and the degree of withdrawal experienced. Gunn (1986) reported that no particular pattern of symptoms emerged following cessation. It appears that withdrawal symptoms may include psychological reactions rather than only physical reactions to nicotine dependence.

Craving for cigarettes in abstaining smokers does not appear to be satisfied by nicotine chewing gum (Hughes and Hatsukami, 1985) although other DSM-III withdrawal-related mood and somatic

symptoms are alleviated (Hughes et al., 1984). Hughes, Hatsukami, Pickens et al. (1984) studied the ability of nicotine gum to alleviate the tobacco withdrawal syndrome (DSMIII criteria). Subjects received either placebo or 2 mg nicotine gum, stopped smoking and returned on the 1st, 2nd and 4th evenings of abstinence for further measurement. Nicotine reduced the increase in irritability, anxiety, difficulty concentrating, restlessness, impatience, and somatic complaints reported by subjects tested with placebo. Reductions in these affect related symptoms were confirmed by scores on the Profile of Mood States Questionnaire. Nicotine (2 mg) did not reduce increases in cigarette craving nor did it have any impact on the more somatic symptoms such as hunger, eating, insomnia, tremulousness or supine heart rate after cessation. Hughes, Hatsukami, Pickens et al. (1984) concluded that the relief of a significant number of withdrawal symptoms by 2 mg nicotine gum suggests that the tobacco withdrawal syndrome is caused in part by nicotine deprivation. West, Jarvis et al. (1984) investigated the effect of nicotine replacement by gum on the nicotine withdrawal syndrome. Subjects were randomly allocated to chew either 2 mg or .5 mg nicotine gum over 24 hours of cigarette abstinence. Characteristic mood and somatic withdrawal symptoms were observed on the low dose (.5 mg) gum including a drop in heart rate. The 2 mg gum alleviated reports of irritability and depression but not hunger or ability to concentrate. Similarly, Schneider, Jarvik and Forsythe (1984), in a placebo-controlled trial of nicotine gum (2 mg), examined withdrawal symptoms for five days of smoking abstinence. Baseline responses on withdrawal items were obtained for comparison to five days of smoking abstinence. After an initial rise in withdrawal, the nicotine group reported

less severity of symptoms compared to the placebo group, as measured by a 14 item scale including measures of withdrawal (anxiety, mood etc.) and craving.

Perhaps nicotine gum, at a 2 mg dose used in the majority of studies does not reach sufficiently high concentrations in the brain necessary to relieve craving. Russell, Feyerabend and Cole (1976) have shown that 4 mg gum is required for plasma nicotine levels to approximate those obtained by smoking. For example, Tonnesen et al. (1988) studied the effectiveness of 2mg and 4mg chewing gum and found that 4mg gum was more effective than 2mg gum in highly dependent smokers and this effectiveness was comparable to that obtained with 2mg gum with medium to low dependence smokers. Similarly, Blondal (1989), in a placebo controlled double-blind study of smokers given either 4 mg or placebo gum, found that highly dependent individuals using the 4 mg gum were thirteen times more likely to abstain at a two year follow up compared to placebo. Therefore the use of 4 mg nicotine polacrilex gum has been shown to substantially aid smoking cessation efforts among highly dependent smokers. As suggested by Nemeth-Coslett, Henningfield et al. (1987), the efficacy of treating tobacco dependence with nicotine gum may be enhanced by increasing the administered dose.

Evidence from nicotine gum studies suggests that highly dependent smokers tend to benefit most from nicotine replacement therapy. A review of placebo-controlled studies which tested the efficacy of nicotine chewing gum suggests that smokers who score high on a measure of nicotine dependence are significantly more likely to benefit from the use of nicotine gum than from placebo (Fagerstrom and Schneider, 1989; Niaura, Goldstein

and Abrahams, 1994).

Considering the ability of nicotine gum to alleviate (at least partially) negative mood states associated with smoking abstinence (Raw, 1985; Lam et al., 1987), it is not surprising that evidence suggests a similarity between the CNS arousal and mood regulating effects of nicotine delivered by nicotine polacrilex (nicotine gum) and those produced by nicotine delivered from inhaled tobacco smoke. Pickworth, Herning and Henningfield (1986) investigated EEG activity following administration of nicotine gum in nicotine deprived subjects. Following a 12 hour deprivation period, doses of 2 mg and 4 mg nicotine gum significantly increased peak frequencies in the global alpha and beta bands and decreased power in the theta band. These results are consistent with evidence previously reviewed (Herning, Jones and Bachman, 1983) indicating that smoking deprivation in smokers produced increases in theta power which was reversed after acute smoking.

This finding is of theoretical importance in the context of the growing body of literature on replacement therapies for smoking cessation. The rationale for the use of such replacement therapies is to abate initial withdrawal symptoms and avoid further withdrawal by gradually tapering the replacement therapy (Hughes, 1993). Nicotine replacement systems are designed to deliver nicotine otherwise obtained by cigarettes, thereby reducing the severity of nicotine withdrawal symptoms experienced following smoking cessation. However, as reviewed, although evidence has demonstrated that nicotine gum reduces some withdrawal symptoms experienced after smoking deprivation (Russell et al., 1976; Hughes et al., 1984), evidence is mixed concerning its ability to relieve craving

(Hughes and Hatsukami, 1985).

Nicotine transdermal systems contain a rate-controlling membrane designed to regulate delivery of nicotine to the skin, thereby limiting variability in nicotine plasma levels. Not surprisingly, a major distinction between cigarettes and smokeless nicotine delivery systems is the rate of initial nicotine uptake and resultant arterial or venous nicotine concentration levels. In cigarette smoking, puff by puff inhalation of smoke delivers a succession of nicotine "boli" to the lungs and directly to the arterial system resulting in rapid nicotine spikes with peak nicotine blood concentrations being reached by the last puff of a cigarette (Russell, 1976). As nicotine is absorbed directly from the lungs to the arterial system, the delivery of nicotine to the brain after each puff is relatively quick and approximates the lung-to-brain blood flow time. Half-life, the time taken for blood nicotine levels to return within 50 percent of baseline levels has been estimated to be about two hours on average with considerable variability between one and four hours (Benowitz, Jacob et al., 1982). This rapid peaking associated with smoking has not been mimicked by other forms of nicotine delivery. Benowitz et al. (1988) found that relative to smoking, the absorption of nicotine from smokeless tobacco and nicotine gum, in contrast, results in lower blood concentrations which are slower to rise and longer to eliminate. Due to continued absorption, blood levels of nicotine fall more slowly after use of smokeless tobacco (chewing tobacco) or nicotine gum in comparison to cigarette smoking (Benowitz, Porchet, Sheiner and Jacob, 1988).

A series of experiments have investigated blood nicotine concentrations from nicotine replacement systems. Benowitz et al. (1987)

studied blood nicotine concentrations from chewing 2 or 4 mg gum and found that nicotine absorption from gum is gradual with continued release throughout the chewing period. When 2 mg gum was used regularly throughout the day, levels of blood nicotine reached one to two thirds of the levels observed with smoking. However, even with 4 mg gum, blood levels of nicotine were considerably lower than that with the use of tobacco. In a similar study, Benowitz, Chan, Denaro and Jacob (1991) investigated the bioavailability and absorption kinetics of transdermal nicotine delivery systems. In comparison to the nicotine delivery systems (cigarettes, oral snuff, chewing tobacco and nicotine gum) in a previous study by Benowitz et al. (1988), Benowitz, Chan, Denaro and Jacob (1991) found that the transdermal patch system delivers nicotine at a relatively stable rate over prolonged periods of time. A dose of 19 mg nicotine was delivered and reached a gradual maximal rate of absorption between six and twelve hours after application, confirming that transdermal delivery systems result in a different blood concentration-time profile compared to cigarette smoking. In addition, studies investigating the absorption kinetics of NTS following single NTS application indicate a dose-time effect. Gupta, Okerholm et al. (1993) found that after an application of a Nicoderm (NTS) patch designed to deliver 14mg of nicotine per 24 hours, C_{max} (maximal concentration) and t_{max} (time to reach maximal concentration) were 12.2 ng/ml and 4.4 hours, respectively. In a similar study by Gupta, Benowitz et al. (1993) an application of an NTS patch delivered 21 mg of nicotine per 24 hours and C_{max} and t_{max} were 18.1 ng/ml and 6.2 hours, respectively. In contrast, Gorsline, Gupta et al. (1993) investigated the dose-plasma nicotine relationship of nicotine

delivered from Nicoderm (NTS) at doses of 7, 14 and 21 mg and found that time to reach peak concentration was similar for all three dosages, indicating no change in nicotine absorption with increasing dose.

Gorsline, Benowitz et al. (1992) compared plasma nicotine concentrations for nicotine transdermal system, cigarette smoking and nicotine polacrilex. NTS (21 mg/day) provided sustained plasma nicotine concentrations that were lower than usual cigarette smoking and within the range achieved by repeated administration of nicotine gum (2 mg, 1 piece every 100 min.). A single application of a transdermal nicotine system releasing 21 mg/day resulted in plasma nicotine concentrations of about half those of ad libitum smoking over fifteen hours. In a review of laboratory data, Henningfield and Keenan (1993) reported that nicotine polacrilex and transdermal systems deliver nicotine more slowly and at lower dose levels than tobacco based forms. Serum nicotine levels during nicotine patch therapy was also investigated by Hurt et al. (1993). Treatment with a 22 mg nicotine patch resulted in lower serum nicotine levels than that observed when the subjects were smoking.

Briefly, a review of clinical NTS studies suggests the use of transdermal nicotine, in comparison to a placebo condition, approximately doubles the chances of successful smoking abstinence (Abelin et al., 1989; Hurt et al., 1990; Tonnesen et al., 1991). There is also evidence indicating that transdermal nicotine alleviates not only mood disturbances but also more critical and enduring craving for cigarettes (Transdermal Nicotine Study Group, 1991). In a recent study by Norregaard, Tonnesen et al. (1993) craving for cigarettes was the most often self-reported reason for relapse in smoking cessation with placebo patches.

In addition to a reduction of cigarette craving, evidence also suggests a dose-response effect of nicotine transdermal systems. The Transdermal Nicotine Study Group (1991) investigated the efficacy of a six week transdermal nicotine system which delivered nicotine at rates of 21, 14, or 7 mg/day and found a dose-response effect with abstinence rates of 61%, 48% and 27% respectively. Combined nicotine withdrawal symptom scores and nicotine craving scores were significantly lower for 21 and 14 mg than for placebo at every week. The 21 mg patch was superior to the other active doses in reducing craving during the first three weeks of abstinence.

Fiore, Jorenby et al. (1992) completed a comprehensive review of transdermal nicotine treatment for tobacco dependence. Their review of clinical trials using placebo-controlled, double blind methodology with at least six months of follow up treatment found that nicotine patches produce smoking cessation rates about double those of placebo controlled subjects. In addition, nicotine patches appeared to reduce some nicotine withdrawal symptoms. For example the patch consistently appeared to reduce craving for cigarettes and negative affect but tended not to reduce hunger or weight gain. In a similar review, Palmer, Buckley and Faulds (1992) reported that in the majority of trials, transdermal nicotine significantly reduced craving for cigarettes as measured by self-reports. In addition, trials which combined withdrawal symptoms into an overall score reported that transdermal nicotine significantly reduced this score (Transdermal Nicotine Study Group, 1991). However where the effect of transdermal nicotine systems on withdrawal symptoms were analyzed separately, significant effects were observed for some symptoms but not others. For

example, although transdermal nicotine treatment had no effect on increases in appetite and habit withdrawal (i.e. finger, mouth manipulation), negative affect symptoms were reduced and improved concentration was reported (Rose et al., 1990).

In summary, the empirical literature investigating the effect of transdermal nicotine replacement suggests an underlying physiological response similar to smoking. Although, to date, the majority of transdermal nicotine studies are clinical cessation trials, the transdermal patch has been shown to a) produce blood levels of nicotine similar to smoking and b) mediate negative affective states believed to be related to smoking withdrawal, suggesting a similar effect on electrocortical arousal as measured by EEG recording techniques which, to date, has not previously been explored.

Objectives

Smokers believe smoking is pleasurable, helps them relax and reduces negative emotions. Experimental studies, the majority of which were conducted in cigarette deprived smokers, tend to support the view that nicotine and other means of nicotine administration exert mood regulating effects with the predominant outcome being a reduction in negative affect. Although it is uncertain as to whether the mood modulating effects of smoking are dependent upon smoking deprivation, investigations into the mechanisms underlying the attraction of the smoking habit have predominantly focused on the CNS arousal model which postulates that smoking/nicotine - induced increases and decreases in emotionality are associated with increases and decreases in cortical arousal,

respectively. To date, the known electrocortical effects of smoking/nicotine in humans can best be described as being psychostimulating in action. Paradoxically, in contrast to the EEG-stimulus profile observed with cigarette smoking, the predominant psychological effects of smoking appear to be sedational in nature and these effects are particularly evident in smoking cessation studies which have utilized nicotine replacement strategies.

Although the few existing studies to date indicate that nicotine gum administration results in a electrocortical response pattern similar to that observed with cigarette smoking, there has been no systematic attempt to examine the CNS arousing effects of the transdermal nicotine patch or the relationship of these CNS effects to the relatively consistent reductions in negative affect observed with this nicotine replacement strategy. As this research will provide valuable insight into motivational processes underlying cigarette smoking, the general objective of this study is to examine and isolate the putative role of nicotine in the smoking habit via an examination of the effects of transdermal nicotine patch administration on electrocortical arousal and self-reported mood changes and their relationships.

Based on previous smoking-related EEG and mood studies, it is hypothesized that compared to a placebo patch, a nicotine patch will result in a psychostimulant-like EEG profile characterized by a shift in power from low to higher alpha 2 frequencies and beta frequencies and that the nicotine patch will attenuate negative affect responses observed with placebo patch. Specifically, day-long smoking deprivation should be accompanied by significant increments in tension-anxiety, anger-hostility

POMS dimensions and may also include increased scores in confusion-bewilderment, fatigue-inertia and depression-dejection dimensions as well as a decreased score in vigor-activity (a positive affect dimension). Following administration of the patch, one would predict a reduction of tension-anxiety, anger-hostility and perhaps reduced scores in confusion-bewilderment, fatigue-inertia and depression-dejection dimensions as well as an increase in vigor-activity dimension score. Although evidence of smoking-related regionalized cortical effects are more tenuous, it is further hypothesized that smoking alpha 2 and beta increments observed with the nicotine patch will be more evident in frontal recording sites than in posterior recording sites and more evident in the right hemisphere than in the left hemisphere. Finally, it is hypothesized that the regionalized psychostimulant actions of the nicotine patch will be related to reductions in negative affect induced by the patch, with increased right hemisphere activation (relative to left) being positively correlated with decreasing negative affect.

Method

1. Experimental Subjects

Sixteen smokers responding to a newspaper advertisement were used in this study. The sample size $n = 16$ was chosen to give .80 power with an alpha of .05 for a two tailed test to detect an effect size $d = 1.0$ (Cohen, 1988). Subjects were screened initially by telephone and then by a medical exam prior to entry into the study. Telephone screening involved questioning potential subjects on smoking and alcohol/drug history,

medication use and physical/neurological illnesses. The Fagerstrom Tolerance Questionnaire (Fagerstrom, 1978) (a score of 7 or more indicates a subject is significantly dependent on nicotine - see Appendix I) and DSM III-R criteria for tobacco withdrawal (Appendix II) were administered so as to obtain an indirect estimate of their degree of dependence/tolerance to cigarettes (Fagerstrom, 1978). The medical exam, carried out by an ROH physician, following successful telephone screening, ensured that there were no contraindications to NTS treatment. The following inclusion/exclusion criteria were employed in this study.

(i) Inclusion Criteria:

1. male;
2. right handed;
3. 20 to 49 years of age;
4. current smoking history of 5 or more consecutive years;
5. presently smoking, with reported inhalation, a minimum of 20 cigarettes per day with cigarettes containing nicotine yields of at least 0.5mg (range 0.9 - 1.2mg).;
6. a score of 7 or higher on the Fagerstrom Tolerance Questionnaire;
7. experience of a previous withdrawal episode as measured by DSM III-R;
8. medical history and physical examination including electrocardiogram with no serious abnormalities, standing and supine blood pressure and heart rate within normal range;
9. judged to be reliable in study requirements;
10. voluntary participation as per consent form.

(ii) **Exclusion Criteria:**

1. present or past psychiatric history (according to DSM III-R criteria) including alcohol/drug abuse;
2. use of prescription and non-prescription medications that may significantly affect CNS functions and/or interact with nicotine administration;
3. cardiovascular or peripheral vascular disease;
4. history of allergic reactions and skin disorders;
5. neurological disorders including cerebral vascular pathology and head trauma causing a period of unconsciousness for a period of one hour or more;
6. physical illness including renal or hepatic deficiency, endocrine disease, peptic ulcer disease, evidence/history of cardiovascular and/or peripheral vascular disease (eg. myocardial infarction, serious arrhythmias or severe angina pectoris).

2. **Experimental Design**

Subjects were tested within a 2 x 4 repeated measures randomized block experimental design where dependent measures were sampled during two nicotine treatments (a placebo NTS patch and an active nicotine NTS patch) and, within each treatment, at five separate time intervals (pre NTS patch and 1, 2, 3, 4 hours post NTS patch). All subjects were tested in both placebo and active NTS conditions with each subject serving as his own control. Half of the subjects were randomly selected to be administered the placebo NTS treatment first and active treatment second while the remaining half of the subjects received the treatments in reverse

order. In order to control for possible carry-over drug effects, test sessions were separated by a minimum of three days.

3. Study Procedure

i) Study Overview

Following a successful telephone screening and medical examination, subjects attended one afternoon orientation session to familiarize them with the study procedures and laboratory environment. The orientation session followed a fixed schedule as outlined in Table 1. During the orientation the

Insert Table 1 about here

objective of the study, together with the general procedures were outlined and if the subject agreed to participate a written informed consent was obtained (Appendix IV). In addition, subjects were exposed to the EEG hook-up procedure and instructed on requirements to reduce non-cerebral artifacts during EEG recordings. Subjects also practiced completing self-report questionnaires and at the end of the orientation session, subjects were given appointments and pre-test session instructions (see below) for their two subsequent test dates.

On the morning of each test session, subjects were instructed to arrive at the laboratory by 8:00 am, after having abstained overnight (from 12:00am) from cigarettes, caffeine, alcohol, drugs and food (with the exception of toast and juice recommended as a 'light' breakfast). Subjects were be directed to a sound-attenuated, electrically shielded chamber and

Table 1

Orientation Schedule (Total Time - 2 Hours)

Time	Procedure
1500	Arrival
1500	Briefing and consent
1520	Tour of Facilities (e.g. lounge, w.c., testing area)
1530	EEG hook-up procedure
1545	Instructions re: artifacts
1550	Trial Recording
1610	Trial (POMS) Questionnaires
1620	EEG removal
1630	Questions
	Appointments
	Final Instructions
1645	Departure

seated in a reclining chair and were tested within a fixed procedural schedule as outlined in Table 2. After electrode attachment, subjects

Insert Table 2 about here

underwent baseline measurement of the dependent variables including EEG measurement and self report of mood state. Baseline assessments were followed by application of a placebo or active patch. Subjects were then assessed on the same dependent variables at hourly intervals following patch application to a maximum of four hours. To maintain subject comfort, a light snack was offered following test blocks.

ii) Nicotine Administration

The active nicotine treatment consisted of the Nicoderm (Marion Merrell Dow) patch which delivers a systemic dose of 21 mg/day over 24 hours (recommended initial dose in cessation programs). The Nicoderm patch covers an area of 22 cm², has a total nicotine content of 114 mg, reaches a mean C_{max} of 23 ng/ml with a t_{max} of 4 hours. The placebo nicotine treatment was identical in size and somatosensory characteristics. The patches were applied to a non-hairy area on the upper back (Gorsline et al., 1992). Subjects were prevented from seeing the patches being applied each day and they were unable to distinguish active and placebo patches on application.

Table 2

Test Session Time Schedule

Time	Procedure
0800	Arrival Time
0800-0830	EEG hook-up
0830-0845	Baseline Testing
0845-0850	Patch Administration
0950-1010	Test Block #1
1050-1110	Test Block #2
1150-1210	Test Block #3
1250-1310	Test Block #4
1310-1320	EEG/Patch removal
1330	Departure Time

iii) Self - Reports

Subjective measures of mood state were based on mood dimensions extracted from the Profile of Mood States questionnaire (Mc Nair et al., 1971), which measures six affective dimensions including tension-anxiety, depression-dejection, anger-hostility, vigour-activity and fatigue-inertia. Scores for each dimension were obtained from responses to sixty-five adjectives rated on a five point scale ranging from zero "not at all" to four "extremely" (Appendix III). The POMS questionnaire has demonstrated predictive and construct validity in controlled outpatient drug trials (Mc Nair et al., 1971) and has been shown to be sensitive to mood alterations occurring during smoking cessation (Hatsukami, D.K. et al., 1984; Hatsukami, D.K. et al., 1987; Perkins, K.A. et al., 1993).

A subjective measure of nicotine dependence was assessed only once during subject screening based on the Fagerstrom Tolerance Questionnaire. This eight item paper and pencil test has a scoring range of 0-11 points with a score of zero being indicative of minimum nicotine dependence and a score of 11 being indicative of maximum nicotine dependence. Several studies have suggested that there may be a relationship between the intensity of experienced withdrawal symptoms and total score on this dependence questionnaire (Fagerstrom, 1980; Hughes and Hatsukami, 1986). In addition, the DSMIII-R criteria for tobacco withdrawal were administered once during subject screening to determine whether subjects experienced withdrawal upon previous cessation attempts.

iv) EEG Recording

As illustrated in Figure 1, tin electrodes were attached to six scalp

Insert Figure 1 about here

sites, F3 , F4, C3, C4, P3 and P4 (10-20 international system; Jasper, 1958) using a monopolar montage with active scalp electrodes being referenced to linked earlobes (A1 and A2). The scalp electrode sites, positioned bilaterally along an anterior-to-posterior plane on both left and right hemispheres, were selected so as to monitor activity from homologous hemispheric sites at frontal (F3, F4), central (C3, C4) and parietal (P3, P4) regions.

Additional electrodes were positioned above the supra-orbital ridge and on the external canthus of the right eye to monitor vertical and horizontal ocular activities (Connolly and Kleinman, 1978). Electrode impedances were kept below 5 kohm and electrical signals were amplified with a bandpass of 0.1 to 30.0 Hz. At baseline and at each test block, five minutes of EEG were recorded with subjects semi-reclined in a comfortable chair with their eyes closed. EEG recordings were simultaneously being monitored by video for the purpose of identifying EEG segments with excessive body movements. Additional instructional procedures were passed to the subject before each session in order to reduce recording artifacts. Subjects were informed of the potential contaminating effect of eye, mouth, tongue, facial and respiratory movements as well as motor contractions and they were instructed on methods to reduce these non-cerebral contaminants. Subjects were instructed to relax but to remain

Electrode Montage

Figure 1. Electrode placement for EEG recordings, based on 10-20 system (Jasper, 1958) within a graphic representation of the top of the head (single plane projection). The six recording sites were referenced to linked earlobes (A1+A2).

alert and not to fall asleep during each of the ten minute eyes closed EEG recordings.

v) Data Reduction

(i) EEG

Analog to digital sampling of electrical activity was carried out at 256 Hz and digitized data was stored to disk for later off-line analysis. Digitized EEG and eye movement tracings were visually screened to edit out time segments with ocular and other non-cerebral contaminants. Segments with ocular and EEG voltages equal to or exceeding 100 μ v were excluded from analysis. For each recording period, at least thirty artifact-free two second epochs of EEG activity were submitted to Fast Fourier Transform (FFT) analysis for computation of absolute amplitude in six frequency bands: delta (1 - 3.5 Hz), theta (4 - 7.5 Hz), alpha 1 (8 - 10.5 Hz), alpha 2 (11 - 13.5 Hz), beta 1 (14 - 21.5 Hz), and beta 2 (22 - 29.5 Hz). In addition to absolute amplitude, each band was expressed as relative amplitude by calculating its percentage of the total amplitude across the six bands (e.g. relative delta = $[\text{delta}/(\text{delta} + \text{theta} + \text{alpha 1} + \text{alpha 2} + \text{beta 1} + \text{beta 2})] \times 100$). As recommended by Gasser et al., EEG data was log transformed ($\log(x)$ where x = absolute amplitude and $\log[x/(1-x)]$ where x = relative amplitude in band) to correct for inherent distribution abnormalities (Gasser et al., 1982). To examine 'net' treatment effects, difference scores were derived by subtracting baseline log data from post-patch log data assessed at each of the four hourly time points.

(ii) POMS

As with the EEG data, 'net' effect difference rating scores for each of the six POMS mood dimensions were determined by subtracting baseline scores from post patch application scores at each of the four hourly time points.

4. Statistical Analysis**i) EEG Data**

Univariate repeated measures analyses were corrected for violation of sphericity assumption (Vasey and Taylor, 1987). The study was considered to be confirmatory in nature and all ANOVA probability values were computed with conservative degrees of freedom (Greenhouse-Geisser epsilon correction). Reported p-values are epsilon corrected, but not degrees of freedom. Unless otherwise indicated, statistical analysis was carried out on both absolute amplitude and relative amplitude data for each frequency band as well as on total absolute amplitude summed across the six frequency bands.

Analysis of variance was carried out for baseline data in order to determine whether baseline recordings were similar across testing. Separate 2 (baseline sessions) x 6 (electrode sites: F3, F4, C3, C4, P3, P4) ANOVAs were calculated for each frequency band using baseline data.

For EEG difference data, separate 2 (nicotine: 0 mg vs. 21 mg) x 4 (time: 1, 2, 3, 4 hours) x 6 (electrode sites: F3, F4, C3, C4, P3, P4) repeated measures ANOVA were carried out separately on each amplitude index.

In addition, absolute and relative laterality amplitude ratio scores (calculated as the ratio of left - right/left + right amplitude for all three homologous electrode pairs) were examined for each frequency band. For these ratio scores, negative values are indicative of reduced right hemispheric EEG amplitude, whereas positive values indicate greater relative left hemispheric EEG amplitude. Separate 2 (nicotine: 0 mg vs. 21 mg) x 4 (time: 1, 2, 3, 4 hours) x 3 (site: F3-F4, C3-C4, P3-P4) repeated measures ANOVAs were computed on the ratio scores for each frequency band.

Follow-up post hoc tests of significant ANOVA main effects and/or interactions were carried out using the Tukey test for multiple comparisons with significance levels adjusted for family-wise error.

ii) POMS Data

To test reliability, analysis of variance was carried out for baseline data. Separate simple factorial ANOVAs were calculated for each Profile of Mood States dimension.

As with the EEG data, difference data (i.e. post-patch minus pre-patch data) derived from individual item scores extracted from the POMS questionnaires were submitted to separate 2 (nicotine: 0 mg vs. 21 mg) x 4 (time: 1, 2, 3, 4 hours) repeated measures ANOVA for each of the six mood dimensions.

The relationship between the degree of nicotine induced EEG changes and nicotine-induced affect changes was examined using the Pearson product moment correlation matrix. EEG (absolute and relative) data was averaged across channel, resulting in 24 (six POMS dimensions for each of four hours) correlations for each frequency band. Only frequency bands

exhibiting significant nicotine-induced alterations were included in the correlational analysis.

RESULTS

Data for 16 subjects was included in the present analysis. All subjects were male, right handed, age ($\bar{M} = 29.4$, $\underline{SD} = 9.2$), years smoking ($\bar{M} = 12.8$, $\underline{SD} = 8.8$), number of cigarettes/day ($\bar{M} = 23.0$, $\underline{SD} = 4.0$), nicotine content(mg) ($\bar{M} = 1.1$, $\underline{SD} = 0.1$), FTQ score ($\bar{M} = 7.9$, $\underline{SD} = 1.0$) and conformed to inclusionary/exclusionary criteria outlined above.

(i) EEG

EEG Baseline Data:

Although no differences were observed between the two sessions, analysis of baseline absolute amplitude data revealed a significant main effect of recording site for delta ($\underline{F}(5,75) = 11.70$, $p = .00$), alpha 1 ($\underline{F}(5,75) = 30.75$, $p = .00$), alpha 2 ($\underline{F}(5,75) = 34.42$, $p = .00$), beta 1 ($\underline{F}(5,75) = 8.01$, $p = .00$) and beta 2 ($\underline{F}(5,75) = 3.16$, $p = .04$). Similarly, analysis of baseline relative amplitude data revealed no significant session effect, but a main effect of recording site for all six frequency bands: delta ($\underline{F}(5,75) = 9.18$, $p = .00$), theta ($\underline{F}(5,75) = 10.54$, $p = .00$), alpha 1 ($\underline{F}(5,75) = 20.47$, $p = .00$), alpha 2 ($\underline{F}(5,75) = 22.83$, $p = .00$), beta 1 ($\underline{F}(5,75) = 5.72$, $p = .01$) and beta 2 ($\underline{F}(5,75) = 12.06$, $p = .00$). Figure 2 shows the amplitude spectrum of absolute EEG indices, averaged

Insert Figure 2 about here

Figure 2. Mean baseline EEG absolute amplitude spectrum (averaged across both placebo and nicotine experimental conditions) expressed as a function of six frequency bandwidths for all six electrode sites.

across the two baseline sessions. Note the vertical axis is expressed in analog to digital (A.D.) units specific to the Rhythm 7.1 (Stellate Systems) software utilized. A.D. units are approximately proportional to amplitude expressed in Hz (Stellate Systems, personal communication, May 15, 1995). As can be observed, alpha 1 and alpha 2 amplitude appear increased in central and parietal recording sites compared to frontal recording sites.

EEG Difference Data:

Figures 3 (a-f) and 4 (a-f) show the mean ($\pm$ SD) absolute and

Insert Figures 3-6 about here

relative EEG difference data (for each time period) respectively. Figures 5 and 6 show the same data averaged across the four time intervals.

Analysis of absolute amplitude difference values showed significant nicotine effects for delta ($F(1,15) = 9.40$, $p = .01$), theta ($F(1,15) = 8.91$, $p = .01$) and alpha 2 ($F(1,15) = 7.60$, $p = .01$). As shown in Figure 3, relative to the placebo condition, delta and theta appear reduced whereas alpha 2 appears increased during the nicotine condition. During the placebo condition delta and theta appear increased and alpha 2 appears slightly reduced. Significant time and/or time $\times$ channel interactions were observed for delta, theta, alpha 1 and alpha 2 frequency bands. Analysis of the total EEG absolute amplitude across frequency bands did not reveal any significant effects or interactions.

Figure 3(a-f). Mean ($\pm$ SD) log transformed EEG absolute amplitude (analog to digital units, ;A.D.) difference/change (Δ) scores for nicotine and placebo recording times (1,2,3,4 hours) derived by subtracting baseline pre-drug values from post-drug values.

Figure 3 continued

Figure 3 continued

Figure 4(a-f). Mean ($\pm$ SD) log transformed EEG relative (%) amplitude (analog to digital units, ;A.D.) difference/change (Δ) scores for nicotine and placebo recording times derived by subtracting baseline pre-drug values from post-drug values.

Figure 4 continued

Figure 4 continued

EEG absolute amplitude

Figure 5. Mean ($\pm$ SD) log transformed EEG absolute amplitude (analog to digital units, ;A.D.) difference/change (Δ) scores (post-drug minus pre-drug values) for each of the six frequency bands (delta, theta, alpha1, alpha2, beta1, beta2) collapsed across time.

EEG relative amplitude

Figure 6. Mean (± SD) log transformed EEG relative (%) amplitude (analog to digital units, ;A.D.) difference/change (Δ) scores (post-drug minus pre-drug values) for each of the six frequency bands (delta, theta, alpha1, alpha2, beta1, beta2) collapsed across time.

Follow-up analysis of significant time (delta: $F(3,45) = 4.23, p = .02$; theta: $F(3,45) = 3.29, p = .03$) effects revealed significant differences among cell means for delta between hour one and three ($p \leq .01$), hour one and four ($p \leq .01$) and hour two and three ($p \leq .05$) and for theta between hour one and four ($p \leq .05$). As indicated by Figure 3, mean delta and theta absolute amplitude appeared to increase slightly (relative to baseline) over time. In addition, follow-up of the time $\times$ site interactions (alpha 1: $F(15,225) = 3.04, p = .04$; alpha 2: $F(15,225) = 3.23, p = .02$) failed to indicate any statistically significant differences. However, alpha 1 appeared reduced at P3 ($M = -.035, SD = .165$) and P4 ($M = -.026, SD = .182$) sites during hour three. Again, although not statistically significant, alpha 2 also appeared slightly reduced at P3 ($M = .009, SD = .127$) and P4 ($M = .013, SD = .142$) during hour three compared to frontal and central electrode locations.

Analysis of relative amplitude difference values showed significant nicotine effects for theta ($F(1,15) = 15.37, p = .00$), alpha 2 ($F(1,15) = 26.29, p = .00$) and beta 2 ($F(1,15) = 7.40, p = .02$). As illustrated in Figure 4, nicotine, relative to placebo, appeared to decrease theta and increase alpha 2 and beta 2. During the placebo condition theta appeared to increase and alpha 2 and beta 2 appeared to decrease. No other significant main effects or interactions were observed.

Laterality Ratio Scores:

Analysis of EEG absolute amplitude ratio scores (frontal, central and parietal) indicated a significant main effect of site for alpha 2 ($F(2,30) = 4.97, p = .02$). Follow-up analysis revealed ratios for frontal and central electrode pairs appeared to be significantly different from parietal ratios

(frontal vs. parietal; $p \leq .01$, central vs. parietal; $p \leq .01$) for alpha 2. At both frontal and central regions, but not parietal regions, alpha 2 amplitude ratios tended to become less negative (frontal $\underline{M} = .005$, $\underline{SD} = .016$; central $\underline{M} = .002$, $\underline{SD} = .017$) while amplitude became more negative in the parietal region ($\underline{M} = -.005$, $\underline{SD} = .020$).

Analysis of EEG relative amplitude ratio scores indicated a significant main effect of site for delta ($F(2,30) = 4.12$, $p = .03$) and alpha 2 ($F(2,30) = 3.76$, $p = .04$) and a significant nicotine x time interaction for alpha 1. Ratios for frontal and central electrode pairs appeared to be significantly different from parietal ratios (frontal vs. parietal; $p \leq .01$, central vs. parietal; $p \leq .01$). At both frontal and central regions, but not parietal regions, delta amplitude ratios tended to become less negative (frontal $\underline{M} = .005$, $\underline{SD} = .043$; central $\underline{M} = .004$, $\underline{SD} = .053$) while amplitude became more negative in the parietal region ($\underline{M} = -.020$, $\underline{SD} = .055$). In addition, ratios for frontal and parietal electrode pairs were found to be significantly different (frontal vs. parietal; $p \leq .01$) for alpha 2. At frontal regions, alpha 2 amplitude ratios tended to become more negative ($\underline{M} = -.004$, $\underline{SD} = .017$) while amplitude became less negative ($\underline{M} = .005$, $\underline{SD} = .027$) in the parietal region.

Follow-up analysis of the significant nicotine x site interaction for alpha 1 ratio scores ($F(3,45) = 3.46$, $p = .03$) failed to indicate any statistically significant differences.

(ii) Profile of Mood States (POMS):

POMS Baseline Data:

Analysis of baseline data did not reveal any significant effects. As illustrated in Figure 7, mean baseline scores appear similar across testing

Insert Figure 7 about here

sessions.

POMS Difference Data:

Table 3 shows the mean ($\pm$ SD) POMS ratings at each time point

Insert Table 3 about here

in both placebo and nicotine sessions. Analysis of POMS difference data showed significant nicotine $\times$ time interactions for the fatigue ($F(3,45)=3.88$, $p=.04$) and vigor ($F(3,45)=3.67$, $p=.03$) dimensions. As illustrated by Table 16, nicotine appeared to reduce fatigue and increase vigor across time.

Follow-up analysis of significant nicotine $\times$ hour interactions for fatigue and vigor POMS dimensions indicated no statistically significant difference among cell means. However, although not statistically significant, a general trend was visually observed among cell means - nicotine appeared to reduce fatigue across time, whereas in the placebo condition fatigue increased across time. In addition, nicotine appeared to increase vigor across time wherever vigor decreased across time in the placebo condition.

a)

**Mean POMS Baseline Scores-
Day 1 Experimental Session**

b)

**Mean POMS Baseline Scores-
Day 2 Experimental Session**

Figure 7(a&b). Mean ($\pm$ SD) Profile of Mood States baseline scores for each of the six POMS dimensions (fatigue, vigor, tension-anxiety, depression-dejection, anger-hostility, confusion-bewilderment) during day 1 and day 2 experimental sessions.

Table 3

Mean Change in Profile of Mood States (POMS) Scores for Each Dimension Across Nicotine and Placebo Conditions

Dimension	Time	Nicotine		Placebo	
		<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
tension- anxiety	1	-0.75	4.52	-2.19	4.86
	2	0.06	4.86	-2.44	5.48
	3	0.00	6.59	-1.50	6.58
	4	0.75	6.57	-1.38	7.54
depression- dejection	1	1.00	2.66	-1.31	5.46
	2	0.44	2.73	-1.31	6.39
	3	0.56	3.60	-1.69	6.04
	4	0.69	3.89	-1.44	6.39
anger-hostility	1	0.06	4.37	-1.12	4.87
	2	0.50	5.43	-2.50	4.77
	3	0.69	5.75	-1.62	6.69
	4	0.44	5.42	-1.25	5.80

Note. The values presented are mean difference scores derived by subtracting baseline scores from mood scores sampled at 1,2,3,4 hours after application.

Except for the vigor-activity mood dimension, increasing numerical values reflect a decrease in the strength of the mood dimensions.

Table 3 continued

Dimension	Time	Nicotine		Placebo	
		<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
vigor- activity	1	0.38	6.14	0.94	5.12
	2	0.38	6.67	0.38	4.86
	3	2.06	7.68	0.44	7.00
	4	3.12	8.88	0.75	6.14
fatigue- inertia	1	0.31	6.50	0.62	4.30
	2	0.81	5.18	0.31	5.00
	3	2.56	6.46	0.44	7.17
	4	1.62	7.31	0.81	7.68
confusion- bewilderment	1	-0.06	2.38	0.38	1.71
	2	-0.56	2.10	1.06	3.15
	3	0.31	2.57	-0.12	2.12
	4	-0.44	3.24	0.06	3.26

Note. The values presented are mean difference scores derived by subtracting baseline scores from mood scores sampled at 1,2,3,4 hours after application.

Except for the vigor-activity mood dimension, increasing numerical values reflect a decrease in the strength of the mood dimensions.

(iii) EEG-POMS Correlations:

As illustrated by Table 4, correlational analysis of significant

Insert Tables 4 and 5 about here

nicotine-induced absolute amplitude frequency band changes (delta, theta and alpha 2) and POMS dimensions failed to indicate the presence of any EEG-mood relationships.

As indicated by Table 5, correlational analysis of significant nicotine-induced relative amplitude frequency band changes (delta, theta, alpha 2 and beta 2) and POMS dimensions indicated significant Pearson product moment correlations for the following nicotine condition comparisons: delta and vigor - hour three ($r = .25$, $p = .05$), alpha 2 and vigor - hour two ($r = .29$, $p = .03$) and alpha 2 and depression/dejection - hour four ($r = .28$, $p = .04$). However, given 96 correlations were calculated, these findings may be attributed to chance alone.

DISCUSSION

This confirmatory study, conducted to investigate whether acute transdermal nicotine induced changes in electrocortical activity and subjective ratings of affect is similar to results obtained in earlier smoking studies, specifically, a psychostimulant-like EEG profile characterized by a shift in power from low to higher alpha 2 and beta frequencies. The results

Table 4

Pearson Product Moment Correlation Matrix(r)-

EEG Amplitude and Profile of Mood States (POMS) Change (post-drug
minus pre-drug) Scores For Nicotine Condition

POMS							
band	hour	fatigue	vigor	t/a	d/d	a/h	c/b
δ	1	.11	.03	.01	.02	.06	.01
δ	2	.05	.00	.02	.00	.02	.00
δ	3	.01	.06	.00	.00	.05	.02
δ	4	.02	.02	.04	.21	.08	.07
θ	1	.04	.07	.06	.06	.04	.00
θ	2	.02	.05	.01	.00	.00	.04
θ	3	.03	.07	.06	.01	.00	.03
θ	4	.00	.15	.11	.02	.01	.00
$\alpha 2$	1	.02	.00	.14	.00	.04	.01
$\alpha 2$	2	.00	.15	.08	.06	.00	.04
$\alpha 2$	3	.00	.15	.14	.01	.02	.07
$\alpha 2$	4	.04	.00	.00	.17	.03	.01

Note. Correlational values are only presented for frequency bands which were significantly altered by nicotine administration.

t/a= tension-anxiety

d/d= depression-dejection

a/h= anger-hostility

c/b= confusion bewilderment

Table 5

Pearson Product Moment Correlation Matrix: (r)-EEG Relative Amplitude and Profile of Mood States (POMS) Change (post-drug minus pre-drug) Scores For Nicotine Condition

		POMS					
band	hour	fatigue	vigor	t/a	d/d	a/h	c/b
δ	1	.02	.04	.02	.06	.07	.00
δ	2	.02	.00	.11	.02	.04	.04
δ	3	.07	.25 *	.00	.00	.04	.17
δ	4	.00	.10	.12	.16	.14	.02
θ	1	.08	.01	.00	.05	.07	.00
θ	2	.03	.06	.04	.02	.00	.04
θ	3	.05	.00	.10	.02	.00	.01
θ	4	.07	.00	.09	.03	.00	.07
$\alpha 2$	1	.02	.04	.10	.00	.08	.04
$\alpha 2$	2	.07	.29 *	.09	.07	.00	.03
$\alpha 2$	3	.12	.22	.20	.00	.03	.00
$\alpha 2$	4	.14	.16	.03	.28 *	.02	.05
$\beta 2$	1	.05	.02	.02	.14	.01	.00
$\beta 2$	2	.05	.03	.18	.00	.00	.09
$\beta 2$	3	.01	.03	.00	.03	.00	.01
$\beta 2$	4	.00	.00	.04	.02	.00	.03

(* $p \leq .05$)

Note. Correlational values are only presented for frequency bands which were significantly altered by nicotine administration.

t/a= tension-anxiety

d/d= depression-dejection

a/h= anger-hostility

c/b= confusion-bewilderment

of the present study appear to confirm the psychostimulant-like EEG profile reported previously with smoke-inhaled nicotine studies. Relative to the placebo patch, the 21 mg nicotine patch reduced slow wave band (delta and theta) amplitude and increase alpha 2 and beta 2 amplitude. Conversely, slow wave amplitude appeared to increase while alpha 2 and beta 2 amplitude appeared reduced in the placebo condition, a trend which is consistent with earlier acute smoking deprivation studies.

Tobacco smoking has been reported to produce asymmetric hemispheric brain effects (Gilbert, 1987; Gilbert et al., 1989; Norton et al., 1992), specifically, nicotine tends to increase activation (i.e. reduced alpha) of the right hemisphere relative to the left hemisphere in non-stress situations and the converse tends to occur during stressful situations. However, in this study, laterality ratio score analysis (ratio of left - right/left + right amplitude - both absolute and relative) provides no support for nicotine's putative asymmetric effect on electrocortical activity. The main effect of site for delta and alpha 2 laterality ratio scores suggest that delta and alpha2 activity appeared to demonstrate some cortical asymmetry which did not appear to be specific to the nicotine condition.

Although not statistically significant, the POMS data tended to indicate the presence of a general nicotine trend among specific mood dimensions. In general, nicotine tended to non-significantly reduce fatigue and increase vigor across time, while placebo appeared to increase fatigue and decrease vigor across time. These tentative observations suggest that nicotine primarily affects dimensions related to vigilance (fatigue and vigor) and not other negative affect dimensions (depression-dejection, anger-hostility, confusion-bewilderment, tension-anxiety).

Smoking reverses a state of cortical hypoarousal induced by tobacco abstinence and EEG slowing observed with tobacco deprivation may be correlated with decreased vigilance and attention that are characteristic of tobacco deprivation.

The efficacy of transdermal nicotine in alleviating withdrawal symptoms has been assessed in a number of trials using various methods, most often by combining several symptoms into a withdrawal symptom score ranging from zero (no withdrawal symptoms) to 4 or 6 (severe withdrawal symptoms). Several studies employing this method reported that transdermal nicotine significantly reduced this score (Fagerstrom et al., 1991; Transdermal Nicotine Study Group, 1991). Another method of assessment - analysis of individual withdrawal symptoms or related groups - has demonstrated significant effects for some symptoms, but not for others. For example, transdermal nicotine has been reported to have no effect on increases in appetite and habit withdrawal (finger, mouth manipulation), whereas negative affect symptoms (tenseness, irritability) were significantly attenuated as well as decreased concentration caused by smoking cessation (Rose et al., 1990). The present mood trend suggests that nicotine, in this modality - dissociated from sensory and behavioral cues associated with cigarette smoking - may primarily mediate affect related to vigilance. In contrast, although speculative at this point, emotionally negative affect dimensions may be partially mediated by behavioral and sensory cues typically associated with smoking.

In addition, correlations between POMS and EEG data in this study suggest that nicotine induced changes in delta and alpha 2 amplitude (a decrease and increase in amplitude respectively) may be related to changes

in affect in the following dimensions: vigor (delta: $\underline{r} = .25$, $p = .05$; alpha 2: $\underline{r} = .29$, $p = .03$) and depression-dejection (alpha 2: $\underline{r} = .28$, $p = .04$). Both major depression and depressive symptoms are reportedly associated with cigarette smoking (Hughes, J.R., Hatsukami, D.K. et al., 1986; Glassman, A.H. et al., 1990; Kendler, K.S. et al., 1993)– an association which remains after anxiety disorders and alcoholism are controlled for (Breslau, N. et al., 1991; Kendler, K.S. et al., 1993). In addition, the association between release of dopamine in the nucleus accumbens and reward mechanisms in the brain has been repeatedly documented. Evidence to date suggests nicotine's ability to augment dopaminergic reward systems may act as the underlying neuropharmacological basis in the association between cigarette smoking and depression.

Of particular interest is a growing body of literature suggesting that the two hemispheres are differentially lateralized for the processing of positive and negative affective stimuli – observed predominantly in the frontal region. Depressed individuals have been reported to exhibit less left sided frontal activation (i.e. more alpha activity) than normal controls (Henriques and Davidson, 1990) and a decrease in right sided alpha (Tucker et al., 1981). Although not confirmed by present laterality ratio findings, reports of the potential therapeutic effects of smoking suggest that nicotine may serve to modulate cortical areas which may be associated with depression and, and consequently utilized by smokers as a tool for emotional control (Henningfield, 1984; Seltzer and Oechsli, 1985).

These EEG-mood findings must be interpreted within the limiting boundaries of the experimental paradigm in which they were observed.

The present study required smokers to wear a 21 mg/day Nicoderm patch after one night of smoking abstinence. There are some design and procedural limitations which one should be cognizant of when attempting to generate hypotheses from the acquired data. First, subjects in the present study are heavy smokers, believed to be sufficiently tobacco dependent to demonstrate withdrawal symptoms upon cessation of smoking. The Fagerstrom Tolerance Questionnaire was used as a measure of dependence as well as DSMIII-R criteria for tobacco withdrawal. Caution should be exercised when attempting to extrapolate results to less dependent populations. Although evidence suggest that nicotine's electrocortical effects may also apply to non-dependent (Kumar et al., 1978; Knott, 1988) and non-smoker populations (Kumar, 1979), this has not - to date - been examined within the present NTS modality.

Second, although nicotine administration on its own has been shown to produce EEG effects similar to those produced by smoking (Pickworth et al., 1986), the pharmacokinetic profiles are quite different for the two routes of administration. The major nicotine replacement methods which have been developed (nicotine gum and the transdermal patch) have been found to match the plasma nicotine plateau found after smoking, but not the rapid nicotine "spike" characteristic of tobacco smoking. In addition, plasma nicotine concentration studies have shown that rate controlled nicotine transdermal systems provide sustained plasma nicotine concentrations that are lower than usual cigarette smoking (Gorsline, Benowitz et al., 1992). Average plasma nicotine concentrations from Nicoderm (21 mg/day dose) are approximately 17 ng/ml, whereas half-hourly smoking of cigarettes produces average plasma nicotine

concentrations of 44 ng/ml (Benowitz, 1988). Recently, plasma levels of nicotine have been correlated with EEG effects (Domino, Matsuoka and Kadoya, 1995; Kadoya, Domino and Matsuoka, 1994). At concentrations lower than 10 ng/ml, delta, theta and alpha 1 activity tend to decrease. At least 10 ng/ml of plasma nicotine is needed to increase alpha 2 and beta activity and higher than 15 ng/ml there is a decrease in alpha 2 (relative to 10 ng/ml), but a somewhat greater increase in beta activity.

Another cautionary restriction is the dosing paradigm utilized in the present study. An acute, single test dose paradigm was employed in the present study. Without repeated dosing, it is not clear whether nicotine's effects on electrocortical arousal will be subject to habituation over time.

In addition, early studies on the effects of smoking and nicotine followed the classical psychopharmacological paradigm of testing the effects of smoking on 'nicotine free' subjects, after 10 - 12 hours of smoking abstinence. Consequently, any changes in state were typically viewed as a reversal of nicotine withdrawal by smoking. Is it necessary to have a period of smoking deprivation for these effects to occur? There exists a growing body of literature supporting the theory that nicotine induced changes in cortical activity, performance, mood etc., may be independent of nicotine withdrawal. Nicotine's stimulant- like effect has been demonstrated with intravenous nicotine (Kumar et al., 1978), cigarette smoking (Knott, 1988) as well as in non-deprived smokers (Knott and Venables, 1977) and non-smokers (Kumar, 1979).

A final cautionary restriction is the absence of a behavioral anchor in the present experimental paradigm. Considering smoking has been reported as vigilance enhancing, a reaction time (RT) measure may

complement EEG and affect measures utilized in the present study.

Traditionally, RT tasks have been designed to separate psychological processes which take place between the time that a stimulus appears and the time that a response is given.

Given these cautionary restrictions, one might attempt to formulate hypotheses regarding the relevance of the observed EEG findings to smoking motivation. The results of the present investigation support the theory that smoking related changes in EEG are primarily a function of the nicotine absorbed into the system and not necessarily a function of other smoking components. The transdermal patch has made it technically possible to examine the dissociation of sensory cues from pharmacologic effects of nicotine. As indicated previously, within the context of motivational theories, it appears that nicotine may function to maintain the smoking habit whereas social, psychological and individual state factors may act as modulators of smoking behaviour.

Future NTS research should attempt to answer the important question previously discussed - Are nicotine induced changes in cortical activity, performance and mood independent of individual state factors, i.e. non-dependent smokers and non-smokers? Smoking has been reported to significantly increase dominant alpha frequency in deprived smokers to a level comparable to post-smoking values of non-smokers and non-deprived smokers (Knott and Venables, 1977). Although previous research suggests nicotine's effects may be independent of individual state factors, it is necessary to repeat the present NTS study utilizing dependent, minimally dependent and/or non-smokers, thereby enabling comparisons to be made across three different levels of dependence.

In addition, evidence suggests - in tobacco dependent individuals - nicotine abstinence can produce enhancement in performance on tasks requiring attention and vigilance. Both cigarettes and nicotine administration favourably affect mental efficiency as illustrated by improvements in: vigilance, selective attention, reaction time, learning and problem solving (Wesnes and Warburton, 1983). A corollary hypothesis might predict a positive correlation between nicotine patch induced EEG activity and task performance measured via evoked potential recording techniques. Callaway (1983) developed a serial information processing model (The Stimulus Evaluation/Response Selection Task, S.E/R.S.) useful for studying the effects of drugs on human cognition. The use of both reaction time and event-related potential (ERP) latency provides insight into information processing as well as a behavioral measure (RT) associated with vigilance.

Future investigations into the effect of acute transdermal nicotine on electrocortical arousal may wish to consider an additional factor which may be of interest. Although it is speculative at this point to consider the effect of chronotype on electrocortical activation, recent evidence suggests the importance of considering chronotype as a contributory factor in a multi-causal model of psychostimulant consumption (Adan, 1994). Evening-types have been reported to consume more nicotine per day (17.37 mg) compared to morning (6.62 mg) and neither-types (11.22 mg). Therefore, a corollary hypothesis might predict a positive correlation between chronotype and electrocortical activity- strongest among evening-types.

In summary, this study confirms the persistence of smoking related EEG changes and extends these results to experimental paradigms in which the pharmacologic effects of nicotine are dissociated from sensory and behavioral cues typically associated with smoking. Consequently, this confirmatory investigation provides insight into the dynamics of nicotine induced electrocortical arousal which will be useful in generating specific hypotheses on the brain's response to nicotine, its relationship to the motivation underlying the habit as well as its relevance in the development of effective smoking cessation strategies. A better understanding of the underlying mechanisms will aid in the development of more sophisticated treatment techniques than are currently available.

References

- Abelin, T., Muller, P., Buehler, A., Vesanen, K. and Inhof P. R. (1989). Controlled trial of transdermal nicotine patch in tobacco withdrawal. The Lancet, 1989(1), 7-10.
- Armitage, A. K. (1979). An action of nicotine on transmission to the superior cervical ganglion of the cat. In A. Redmond and C. Izard (Eds.), Electrophysiological Effects of Nicotine. Amsterdam: North Holland, pp. 5-14.
- Armitage, A. K., Hall, G. H. and Sellers, L. M. (1969). Effects of nicotine on electrocortical activity and acetylcholine release from the cat cerebral cortex. British Journal of Pharm Chemo, 35, 152-160.
- Ashton, H., Marsh, V. R., Millman, J. E., Rawlins, M. D., Telford, R. and Tompson, 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.
- Ashton, H., Millman, J. E., Telford, R. and Tompson, J.W. (1973). Stimulant and depressant effects of cigarette smoking on brain activity in man. British Journal of Pharmacology, 48, 715-717.
- Ashton, H. and Golding, J. F. (1989). Smoking: motivation and models. In T. Ney and A. Gale (Eds.), Smoking and Human Behavior (pp. 21-56). Chichester: Wiley.
- Berger, H. (1929). On the electroencephalogram of man. Archiv fuer Psychiatrie und Nervenkrankheiten, 87, 511-570.
- Benowitz, N. L. (1988). Pharmacologic aspects of cigarette smoking and nicotine addiction. The New England Journal of Medicine, 1318-1328.

Benowitz, N. L., Chan, K., Denaro, C. P. and Jacob, P. (1991). Stable isotope method for studying transdermal drug absorption: The nicotine patch. Clinical Pharmacology and Therapeutics, 50(3), 286-293.

Benowitz, N. L., Jacob, P., Jones, R. T. and Rosenberg, J. (1982). Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. Journal of Pharmacology and Experimental Therapeutics, 221, 368-72.

Benowitz, N. L., Jacob, P. and Savanapridi, C. (1987). Determinants of nicotine intake while chewing nicotine polacrilex gum. Clinical Pharmacology and Therapeutics, 41(4), 467-473.

Benowitz, N. L., Porchet, H., Sheiner, L. and Jacob, P. (1988). Nicotine absorption and cardiovascular effects with smokeless tobacco use: Comparison with cigarettes and nicotine gum. Clinical Pharmacology and Therapeutics, 44(1), 23-28.

Benwell, M. (1990). The comparative effects of nicotine with other substances: a focus on brain dopamine systems. In D. M. Warburton (Ed.), Addiction Controversies. New York: Harwood Academic Publishing, pp. 163-184.

Blondal, T. (1989). Controlled trial of nicotine polacrilex gum with supportive measures. Archives of Internal Medicine, 149, 1818-1821.

Bozarth, M. A. (1990). Drug addiction as a psychobiological process. In D. M. Warburton (Ed.), Addiction Controversies. New York: Harwood Academic Publishing, pp. 117-162.

Breslau, N., Kilbey, M.M. and Andreski, P. (1991). Nicotine dependence, major depression, and anxiety in young adults. Arch Gen Psychiatry, 48, 1069-1074.

Brown, B. (1968). Some characteristic eeg differences between heavy smoker and nonsmoker subjects. Neuropsychologica, 6, 381-388.

Church, R. E. (1989). Smoking and the human eeg. In T. Ney and A. Gale (Eds.), Smoking and Human Behavior. New York: John Wiley and Sons, pp. 115-140.

Cinciripini, P. M. (1986). The effects on electrocortical arousal in coronary prone and non coronary prone. Psychopharmacology, 90, 522-527.

Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). New York: Lawrence Erlbaum Assoc. Pub.

Cole, H. and Ray, W. (1985). EEG correlates of emotional tasks related to attentional demands. International Journal of Psychophysiology, 3(1), 33-41.

Collet, L. and Duclaux, R. (1987). Hemispheric lateralization of emotions: absence of electrophysiological arguments. Physiology and Behavior, 40, 215-220.

Collins, R. J., Weeks, J. R., Cooper, M. M., Good, P. I. and Russell, R. R. (1984). Prediction of abuse liability of drugs using i.v. self-administration by rats. Psychopharmacology, 82, 6-13.

Connolly, J. F. and Kleinman, K. M. (1978). A single channel method for recording vertical and lateral eye movements. Electroencephalography and Clinical Neurophysiology, 45, 128-129.

Coppola, R. and Herrmann, W. (1987). Psychotropic drug profiles: comparisons by topographic maps of absolute power. Neuropsychobiology, 18, 97-104.

Corrigall, W.A., (1991). Understanding brain mechanisms in nicotine reinforcement. British Journal of Addiction, 86(5), 507-510.

Cummings, K. M., Giovino, G. et. al. (1985). Reports of smoking withdrawal symptoms over 21 day period of abstinence. Addictive Behaviors, 10, 373-381.

Davidson, R. J., Chapman, J. P. and Chapman, L. J. (1987). Task-dependent eeg asymmetry discriminates between depressed and non-depressed subjects. Psychophysiology, 24, 585.

Davidson, R. J. and Fox, N.A. (1982). Asymmetrical brain activity discriminates between positive and negative affective stimuli in human infants. Science, 218(17), 1235-1236.

Davidson, R. J., Schaffer, C. and Saron, C. (1985). Effects of lateralized presentations of faces on self-reports of emotion and eeg asymmetry in depressed and non-depressed subjects. Psychophysiology, 22(3), 353-364.

Davidson, R. J., Schwartz, G. E. et. al. (1979). Frontal versus parietal EEG asymmetry during positive and negative affect. Psychophysiology, 16(2), 202.

Di Chiara, G. and Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proceedings of The National Academy of Science, 85, 5274-5278.

Diagnostic and Statistical Manual of Mental Disorders. (DSMIII-R) 1987 3rd. ed. rev. Washington, D. C. : American Psychiatric Association.

Domino, E. F. (1967). EEG and behavioral arousal effects of small doses of nicotine. Annals of the New York Academy of Sciences, 42, 216-

244.

Domino, E. F. (1973). Neuropsychopharmacology of nicotine and tobacco smoking. In W. L. Dunn (Ed.), Smoking Behavior: Motives and Incentives. Washington: Winston.

Domino, E. F. (1979). Behavioral, electrophysiological, endocrine and skeletal muscle actions of nicotine and tobacco smoking. In A. Redmond and C. Izard (Eds.), Electrophysiological effects of nicotine. Amsterdam: Elsevier, pp. 133-146.

Domino, E. F. and Matsuoka, S. (1991). Effects of tobacco smoking on the topographic eeg. Brain Topography, 3, 248-250.

Domino, E. F., Riskalla, M., Zhang, Y. and Kim, E. (1992). Effects of tobacco smoking on the topographic eeg. Prog. Neuro-Psychopharmacology and Biological Psychiatry, 16, 463-482.

Ehrlichman, H. and Wiener, M. (1980). EEG asymmetry during covert mental activity. Psychophysiology, 17(3), 228-235.

Essman, W. B. (1973). Nicotine related neurochemical changes. In W. L. Dunn (Ed.), Smoking Behavior: Motives and Incentives. New York: Wiley, pp. 51-65.

Eysenck, H. J. (1973). Personality and the maintenance of the smoking habit. In W. L. Dunn (Ed.), Smoking Behavior: Motives and Incentives. New York: Wiley, pp. 113-146.

Fagerstrom, K. O. (1978). Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addictive Behaviors, 3, 235-241.

Fagerstrom, K. O. (1980). Physical dependence on nicotine as a determinant of success in smoking cessation. World Smoking Health, 5, 22-

23.

Fagerstrom, K. O. and Schneider, N. G. (1989). Measuring nicotine dependence: a review of the FTQ. Journal of Behavioral Medicine, 12(2), 159-182.

Fiore, M. C., Jorenby, D. E., Baker, T. B. and Kentford, S. L. (1992). Tobacco dependence and the nicotine patch-clinical guidelines for effective use. Journal of The American Medical Association, 268, 2687-2694.

Gasser, T., Bacher, P. and Mocks, J. (1982). Transformations towards the normal distribution of broad band spectral parameters of the eeg. Electroencephalography and Clinical Neurophysiology, 53, 119-124.

Gilbert, D. G. (1979). Paradoxical tranquilizing and emotion reducing effects of nicotine. Psychological Bulletin, 86(4), 643-661.

Gilbert, D. G. (1987). Effects of smoking and nicotine on EEG lateralization as a function of personality. Personality and Individual Differences, 8, 933-941.

Gilbert, D. G., Robinson, J. H. and Chamberlin, C. L. (1989). Effects of smoking/nicotine on anxiety, heart rate and lateralization of eeg during a stressful movie. Psychophysiology, 26(3), 311-320.

Gilbert, D. G. and Welser, R. (1989). Emotion, anxiety and smoking. In T. Ney and A. Gale (Eds.), Smoking and Human Behavior. New York: Wiley, pp. 171-198.

Glassman, A.H., Helzer, J.E. et al. (1990). Smoking, smoking cessation, and major depression. JAMA, 264, 1546-1549.

Goldberg, S. R., Spearlman, R. D., Goldberg, D. M. (1981). Persistent high rate behavior maintained by intravenous self-administration

of nicotine. Science, 214, 573-575.

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

Gorsline, J., Benowitz, N. L., Gupta, S. K. et. al. (1992). Comparison of plasma nicotine concentrations for nicotine transdermal system (nts), cigarette smoking and nicotine polacrilex. Clinical Pharmacology and Therapeutics, 51(2), 129 [Abstract]

Gorsline, J., Gupta, S. K., et. al. (1993). Steady state pharmacokinetics and dose relationship of nicotine delivered from nicoderm (NTS). Journal of Clinical Pharmacology, 33, 161-168.

Gorsline, J., Okerholm, R. A., Rolf, C. N., Moos, C. D. and Hwang, S. S. (1992). Comparisons of plasma nicotine concentrations after application of nicoderm (nicotine transdermal system) to different skin sites. Journal of Clinical Pharmacology, 32, 576-581.

Gunn, R. C. (1986). Reactions to withdrawal symptoms and success in smoking cessation clinics. Addictive Behaviors, 11, 49-53.

Gupta, S. K., Benowitz, N. L., Jacob, P., Rolf, C. N. and Gorsline, J. (1993). Bioavailability and absorption kinetics of nicotine following application of a transdermal system. British Journal of Clinical Pharmacology, 36, 221-227.

Gupta, S. K., Okerholm, R. A., Coen, P., Prather, R. D. and Gorsline, J. (1993). Single and multiple dose pharmacokinetics of nicoderm (nts). Journal of Clinical Pharmacology, 33, 169-174.

Hatsukami, D. K., Gust, S. W. and Keenan, R. M. (1987). Physiologic and subjective changes from smokeless tobacco withdrawal.

Clin Pharmacol Ther, 41(1), 103-107.

Hatsukami, D. K., Hughes, J. R. and Pickens, R. W. (1985a).
Blood nicotine, smoke exposure and tobacco withdrawal symptoms.
Addictive Behaviors, 10, 413-417.

Hatsukami, D. K., Hughes, J. R. and Pickens, R. (1985b).
Characterization of tobacco withdrawal: physiological and subjective
effects. National Institute on Drug Abuse Research Monograph, 53, 56-67.

Hatsukami, D. K., Hughes, J. R., Pickens, R. W. and Svikis, D.
(1984). Tobacco withdrawal symptoms: an experimental analysis.
Psychopharmacology, 84, 231-233.

Henriques, J. B. and Davidson, R. J. (1988). EEG activation
asymmetries discriminate between nomothymic depressives and normal
controls. Psychophysiology, 25, 453-454.

Henningfield, J. E. (1984). Pharmacologic basis and treatment of
cigarette smoking. Archives of General Psychiatry, 45(12), 24-34.

Henningfield, J. E. and Keenen, R. M. (1993). Nicotine delivery
kinetics and abuse liability. Journal of Consulting and Clinical
Psychology, 61(5), 743-750.

Herning, R. I., Jones, R. T., Bachman, J. (1983). EEG changes
during tobacco withdrawal. Psychophysiology, 20(5), 507-512.

Herrmann, W. (1982). In Eustav Fischer (Ed.),
Electroencephalography In Drug Research. New York: Verlag.

Hughes, J. R. (1993). Pharmacotherapy for smoking
cessation: Unvalidated assumptions, anomalies, and suggestions for future
research. Journal of Consulting and Clinical Psychology, 61(5), 751-760.

Hughes, J. R. and Hatsukami, D. K. (1985). Short-term effects of nicotine gum. National Institute on Drug Abuse Research Monograph, 53, 68-81.

Hughes, J. R. and Hatsukami, D. K. (1986). Signs and symptoms of tobacco withdrawal. Archives of General Psychiatry, 43, 289-294.

Hughes, J. R., Hatsukami, D. K., Pickens, R. W., Krahn, D. Malin, S. and Luknics, A. (1984). Effect of nicotine on the tobacco withdrawal syndrome. Psychopharmacology, 83, 82-87.

Hurt, R. D., Lauger, G. G. et. al. (1990). Nicotine replacement therapy with use of a transdermal nicotine patch—a randomized double-blind placebo-controlled trial. Mayo Clinic Proceedings, 65, 1529-1537.

Hurt, R. D., Dale, L. C., Offord, K. P. et. al. (1993). Serum nicotine and cotinine levels during nicotine patch therapy. Clinical Pharmacology and Therapeutics, 54(1), 98- 106.

Itil, T. M., Utlett, G. A. et. al. (1971). The effects of smoking withdrawal on quantitatively analysed EEG. Clinical Encephalography, 2, 44-51.

Jarvik, M. E. and Hatsukami, D. K. (1989). Tobacco dependence. In T. Ney and A. Gale (Eds.), Smoking and Human Behavior. New York: John Wiley and Sons, pp. 57-68.

Jasper, H. (1958). The ten-twenty electrode system of the international federation. Electroenceph Clin Neurophysiol, 10, 371-375.

Johnston, L. M. (1942). Tobacco smoking and nicotine. The Lancet, 2, 742.

Kelleher, R. T. and Morse, W. H. (1968). Determinants of the specificity of behavioral effects of drugs. Journal of Physiology, Biochemistry and experimental Pharmacology, 60, 1-56.

Kendler, K.S., Neale, M.C., MacLean, C.L. et al. (1993). Smoking and major depression: a causal analysis. Arch Gen Psychiatry, 50, 36-43.

Knapp, D. E. and Domino, E. F. (1962). Action of nicotine on the ascending reticular activating system. International Journal of Neuropharmacology, 1, 333-351.

Knott, V. J. (1979). Psychophysiological correlates of smokers and non smokers: studies on cortical, autonomic and behavioural responsivity. In A. Redmond and C. Izard (Eds.) Electrophysiological effects of nicotine. Amsterdam: Elsevier, pp. 99-116.

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

Knott, V. J. (1989a). Effects of low-yield cigarettes on electroencephalographic dynamics. Neuropsychobiology, 21, 216-222.

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

Knott, V. J. (1990). A neuroelectric approach to the assessment of psychoactivity in comparative substance abuse. In D. M. Warburton (Ed.), Addiction Controversies. New York: Harwood Academic Publishing, pp. 66-89.

Knott, V. J. (1991). Neurophysiological aspects of smoking behavior: a neuroelectric perspective. British Journal of Addiction, 86, 511-515.

Knott, V. J. and Venables, P. H. (1977). EEG alpha correlates of nonsmokers, smokers, smoking and smoking deprivation. Psychophysiology, 14(2), 150-156.

Kolb, B. and Wishaw, I. Q. (1990). Fundamentals of human neuropsychology (3rd. ed.). New York: Freeman and Co.

Kumar, R (1979). Tobacco smoking: tests of the nicotine dependence hypothesis. In A. Remond and C. Izard (Eds.), Electrophysiological Effects of Nicotine. Amsterdam: Elsevier.

Kumar, R., Cooke, E.C., Lader, M.H. and Russell, M.A.H. (1978) Is tobacco smoking a form of nicotine dependence? In: R.E. Thornton (Ed.), Smoking Behaviour: Physiological and Psychological Influences. London: Churchill Livingstone.

Lam, W., Sacks, H. S., Sze, P. C. and Chalmers, T. C. (1987). Meta-analysis of randomised controlled trials of nicotine chewing gum. The Lancet, 2, 27-30.

Lindsley, D. B. (1952). Psychological phenomena and the eeg. Electroencephalography and Clinical Neurophysiology, 4, 443-456.

Lukas, S. E. and Jasinski, D. R. (1983). EEG power spectral effects of intravenous nicotine administration in humans. Federation Proceedings, 42, 1018 [Abstract].

Mc Nair, D. M, Lorr, M. and Droppleman, L. F. (1971). Profile of Mood States. San Diego: Edits/Educational and Industrial Testing Service Inc.

Mangan, G. L. and Golding, J. F. (1984). The Psychopharmacology of Smoking. Cambridge: Cambridge University Press.

Meyers, M. and Smith, B. D. (1986). Hemispheric asymmetry and emotion: effects of nonverbal affective stimuli. Biological Psychology, 22, 11-22.

Nemeth-Coslett, R., Henningfield, J. E., O'Keefe, M. K. and Griffiths, R. R. (1987). Nicotine gum: dose-related effects on cigarette smoking and subjective ratings. Psychopharmacology, 92, 424-430.

Niaura, R, Goldstein, M. G. and Abrams, D. B. (1994). Matching high and low dependence smokers to self-help treatment with or without nicotine replacement. Preventive Medicine, 23, 70-77.

Norregard, J., Tonnesen, P. et. al. (1993). Predictors and reasons for relapse in smoking cessation with nicotine and placebo patches. Preventive Medicine, 22, 261-271.

Norton, R., Brown, K. and Howard, R. (1992). Smoking, nicotine dose and the lateralization of electrocortical activity. Psychopharmacology, 108, 473-479.

O'Connor, K. (1989). Individual differences and motor systems in smoker motivation. In T. Ney and A. Gale (Eds.), Smoking and Human Behavior. New York: John Wiley, pp. 141-170.

Palmer, K, J., Buckley, M. M. and Faulds, D. (1992). Transdermal nicotine - a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. Drugs, 44(3), 498-529.

Perkins, K. A., Grobe, J. E, Epstein, L. H. et. al. (1993). Chronic and acute tolerance to subjective effects of nicotine. Pharmacology, Biochemistry and Behavior, 45, 375-381.

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

Pickworth, W. B., Herning, R. I. and Henningfield, J. E. (1989).
Spontaneous eeg changes during tobacco abstinence and nicotine
substitution in human volunteers. Journal of Pharmacology and
Experimental Therapeutics, 251, 976-982.

Pomerleau, O. F., Fertig, J. B. and Shanahan, S. D. (1983).
Nicotine dependence in cigarette smoking: an empirically based,
multivariate model. Pharmacology, Biochemistry and Behavior, 19, 291-299.

Pomerleau, O. F. and Pomerleau, C. S. (1984). Neuroregulators
and the reinforcement of smoking: towards a biobehavioral explanation.
Neuroscience and Biobehavioral Reviews, 8, 503-513.

Pomerleau, O. F., Scherzer, H. H., Grunberg, N. E. et. al. (1987).
The effects of acute exercise on subsequent cigarette smoking. Journal of
Behavioral Medicine, 10, 117-127.

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

Raw, M. (1985). Does nicotine chewing gum work? British Medical
Journal, 290, 1231-1232.

Robinson, J. H. and Pritchard, W. S. (1992). The role of nicotine in
tobacco use. Psychopharmacology, 108, 397-407.

Robinson, J. H., Pritchard, W. S. and Davis, R. A. (1992).
Psychopharmacological effects of smoking a cigarette with typical 'tar' and
carbon monoxide yields but minimal nicotine. Psychopharmacology, 109(4),
466-72.

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PM-1 3½"x4" PHOTOGRAPHIC MICROCOPY TARGET
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Rose, J.E. and Levin, E.D. (1991). Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. British Journal of Addiction, 86(5), 605-510.

Rose, J. E., Behm, F. and Levin, E. (1992). Role of nicotine dose and sensory cues in the regulation of smoke intake. Pharmacology, Biochemistry and Behavior, 44, 891-900.

Rose, J. E., Tashkin, D. P., Ertle, A., Zinger, M. C. and Lafer, R. (1985). Sensory blockade of smoking satisfaction. Pharmacol Biochem and Behav, 23, 289-293.

Royal Society of Canada (1989). Tobacco, nicotine and addiction. Report by The Ministry of Health, Health Protection Branch.

Russell, M. A. (1976). Tobacco smoking and nicotine dependence. In Research Advances In Alcohol and Drug Problems. Vol 1. R. J. Gibbins ed. New York: Wiley, pp. 1-48.

Russell, M. A., Feyerabend, C. and Cole, P. V. (1976). British Medical Journal, 1, 1043.

Russell, M. A. (1990). The nicotine addiction trap: a forty year sentence for cigarettes. British Journal of Addiction, 85, 293-300.

Russell, M. A., Wilson, C., Feyerabend, C. and Cole, P. V. (1976). Effect of nicotine chewing gum on smoking behavior and as an aid to cigarette withdrawal. British Medical Journal, 2, 391-393.

Saletu, B. (1987). The use of pharmaco-eeg in drug profiling. In I. Hindmarch and P.D. Stonier (Eds.) Human Psychopharmacology - Measures and Methods, Vol 1. New York: Wiley, pp. 173-200.

Schachter, S. (1978). Pharmacological and psychological determinants of smoking. Annals of Internal Medicine, 88, 104-114.

Schiffman, S. M. (1979). The tobacco withdrawal syndrome. National Institute on Drug Abuse Research Monograph, 23, 158-184.

Schiffman, S. M. and Jarvik, M. E. (1976). Smoking withdrawal symptoms in two weeks of abstinence. Psychopharmacology, 50, 35-39.

Schneider, N. G., Jarvik, M. E. et. al. (1983). Nicotine gum in smoking cessation: a placebo controlled double blind trial. Addictive Behaviors, 8, 253-261.

Schneider, N. G., Jarvik, M. E. and Forsythe, (1984). Nicotine vs. placebo gum in the alleviation of withdrawal during smoking cessation. Addictive Behaviors, 9, 149-156.

Seltzer, C. C. and Oechsli, F. W. (1985). Psychosocial characteristics of adolescent smokers before they started smoking: evidence of self selection. Journal of Chronic Disease, 38, 17-26.

Silagy, C., Mant, D., Fowler, G. and Lodge, M. (1994). Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. The Lancet, 343, 139-142.

Silverman, A. R. (1971). Behavior of rats given a smoking dose of nicotine. Animal Behavior, 19, 67-74.

Smith, B., Meyers, M., Kline, R. and Bozman, A (1985). Hemispheric asymmetry and emotion: lateralized parietal processing of affect and cognition. Biological Psychology, 25, 247-260.

Srivastava, E. D., Russell, M. A. H., Feyerabend, C., Masterson, J. G. and Rhodes, J. (1991). Sensitivity and tolerance to nicotine in smokers and nonsmokers. Psychopharmacology, 105, 63-68.

Stepney, R. E. G. (1979). Smoking as a psychological tool. Bulletin of The British Psychological Society, 32, 341-345.

Appendix F continued

and coffee the night before you arrive at the laboratory and also throughout the test sessions.

Possible Risks:

The risks are very slight. Brain wave activity monitoring procedures are similar to those carried out in regular general hospitals except these study procedures use computers for measurement. You may observe a mild temporary skin irritation where the EEG electrode contacts your skin. Abstaining from smoking may provoke psychological discomfort but this will be no more or less than what you have experienced when you try giving up the habit on your own. The risks associated with acute nicotine patch use are negligible compared to chronic tobacco use.

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Date

Signature of Research Subject

Date

Signature of Witness

Appendix A

Fagerstrom Tolerance Questionnaire

1. How many cigarettes a day do you smoke?
2. What brand do you smoke?
3. Do you inhale? Always Sometimes Never
4. Do you smoke more during the morning than during the rest of the day?
5. How soon after you wake up do you smoke your first cigarette?
6. Which cigarette would you hate to give up?
7. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g. in church, at the library, cinema etc.?
8. Do you smoke if you are so ill that you are in bed most of the day?

Appendix B

FTQ Assumptions:

It was hypothesized that nicotine dependence should be related to the following (Fagerstrom, 1978).

1. It was assumed that high frequency of using the drug pointed to more physical dependence.
2. It was assumed that brands which hold a higher dose of nicotine pointed to more physical dependence.
3. Making the nicotine more effective by inhalation pointed to more physical dependence.
4. Smoking more in the morning when the level of nicotine in the body is very low indicated greater physical dependence.
5. Smoking almost directly after getting up in the morning was taken as a sign of physical dependence.
6. Rating the first cigarette in the morning as the most precious one pointed to physical dependence.
7. Little external and relatively internal stimulus control manifested as frequent urges in e.g. churches pointed to more physical dependence.
8. Smoking while ill is taken as a sign of physical dependence.

Scoring the Tolerance Questionnaire

Higher points are always given for answers indicating more addiction. In the first question smokers are divided as light <15, moderate 16-25, and heavy >26 smokers. In the second question, the brands are classified into three categories with low, medium and high nicotine level. In the third question the frequency of inhalations are divided into three categories. The rest of the questions are scored zero or one, with one point for yes answer on question 4. In the fifth question one point is assigned to smoking within 30 min. In the sixth question one point is assigned for answering "the first cigarette in the morning." The seventh and eighth questions are scored with one point for yes answer.

The questionnaire has a range of 0-11 points, with 0 indicating minimum physical dependence and 11 points maximum physical dependence (Fagerstrom, 1978; Fagerstrom and Schneider, 1989).

Appendix B continued

Question	Answers	Points
1. How many cigarettes a day do you smoke?	15 or less	0
	16-25	1
	26 or more	2
2. What brand do you smoke?	0.9 mg or less	0
	1.0-1.2 mg	1
	1.3 mg or more	2
3. Do you inhale?	Never	0
	Sometimes	1
	Always	2
4. Do you smoke more during the morning than during the rest of the day?	Yes	1
	No	0
5. How soon after you wake up do you smoke your first cigarette?	Within 30 min	1
	After 30 min	0
6. Which cigarette would you hate to give up?	The first one in the morning	1
	Any other	0
7. Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes	1
	No	0
8. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

Appendix C

Diagnostic Criteria for Nicotine Withdrawal (DSMIII-R)

- A. Daily use of nicotine for at least several weeks.
- B. Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 hours by at least four of the following signs:
 - (1) craving for nicotine
 - (2) irritability, frustration, or anger
 - (3) anxiety
 - (4) difficulty concentrating
 - (5) restlessness
 - (6) decreased heart rate
 - (7) increased appetite or weight gain

Appendix D

NAME _____

DATE _____

SEX

Male M

Female F

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY

The numbers refer to these phrases

- 0 Not at all
1 A little
2 Moderately
3 Quite a bit
4 Extremely

IDENTIFICATION

0	1	2	3	4	5	6	7	8	9
0	1	2	3	4	5	6	7	8	9
0	1	2	3	4	5	6	7	8	9
0	1	2	3	4	5	6	7	8	9
0	1	2	3	4	5	6	7	8	9
0	1	2	3	4	5	6	7	8	9
0	1	2	3	4	5	6	7	8	9
0	1	2	3	4	5	6	7	8	9
0	1	2	3	4	5	6	7	8	9
0	1	2	3	4	5	6	7	8	9

1 Friendly	0 1 2 3 4	21 Hopeless	0 1 2 3 4	45 Desperate	0 1 2 3 4
2 Tense	0 1 2 3 4	22 Relaxed	0 1 2 3 4	46 Sluggish	0 1 2 3 4
3 Angry	0 1 2 3 4	23 Unworthy	0 1 2 3 4	47 Rebellious	0 1 2 3 4
4 Worn out	0 1 2 3 4	24 Spiteful	0 1 2 3 4	48 Helpless	0 1 2 3 4
5 Unhappy	0 1 2 3 4	25 Sympathetic	0 1 2 3 4	49 Weary	0 1 2 3 4
6 Clear-headed	0 1 2 3 4	26 Uneasy	0 1 2 3 4	50 Bewildered	0 1 2 3 4
7 Lively	0 1 2 3 4	27 Restless	0 1 2 3 4	51 Alert	0 1 2 3 4
8 Confused	0 1 2 3 4	28 Unable to concentrate	0 1 2 3 4	52 Deceived	0 1 2 3 4
9 Sorry for things done	0 1 2 3 4	29 Fatigued	0 1 2 3 4	53 Furious	0 1 2 3 4
10 Shaky	0 1 2 3 4	30 Helpful	0 1 2 3 4	54 Efficient	0 1 2 3 4
11 Listless	0 1 2 3 4	31 Annoyed	0 1 2 3 4	55 Trusting	0 1 2 3 4
12 Peeved	0 1 2 3 4	32 Discouraged	0 1 2 3 4	56 Full of pep	0 1 2 3 4
13 Considerate	0 1 2 3 4	33 Resentful	0 1 2 3 4	57 Bad-tempered	0 1 2 3 4
14 Sad	0 1 2 3 4	34 Nervous	0 1 2 3 4	58 Worthless	0 1 2 3 4
15 Active	0 1 2 3 4	35 Lonely	0 1 2 3 4	59 Forgetful	0 1 2 3 4
16 On edge	0 1 2 3 4	36 Miserable	0 1 2 3 4	60 Carefree	0 1 2 3 4
17 Grouchy	0 1 2 3 4	37 Muddled	0 1 2 3 4	61 Terrified	0 1 2 3 4
18 Blue	0 1 2 3 4	38 Cheerful	0 1 2 3 4	62 Guilty	0 1 2 3 4
19 Energetic	0 1 2 3 4	39 Bitter	0 1 2 3 4	63 Vigorous	0 1 2 3 4
20 Panicky	0 1 2 3 4	40 Exhausted	0 1 2 3 4	64 Uncertain about things	0 1 2 3 4
		41 Anxious	0 1 2 3 4	65 Bused	0 1 2 3 4
		42 Ready to fight	0 1 2 3 4		
		43 Good natured	0 1 2 3 4		
		44 Gloomy	0 1 2 3 4		

MAKE SURE YOU HAVE
ANSWERED EVERY ITEM.

POMS 021

Appendix E

Profile of Mood States Scoring

Six POMS dimensions (McNair, 1971):

1. Tension-Anxiety
2. Depression-Dejection
3. Anger-Hostility
4. Vigor-Activity
5. Fatigue-Inertia
6. Confusion-Bewilderment)

To obtain a score for each of the following six POMS dimensions sum the responses obtained for the adjectives defining the factor. All items in each factor are keyed in the same direction, with two exceptions:

- a) "Relaxed" in Tension-Anxiety Scale
- b) "Efficient" in Confusion Scale

These two items receive negative weights.

Appendix F

INFORMED CONSENT FOR EXPERIMENTAL SUBJECTS

Title of Study: Acute Effects of Transdermal Nicotine on Arousal and Mood During Short-term Smoking Deprivation

Principal Investigators: M. A. Bosman, BScH

Co-Investigators: Dr. V. Knott-Advisor and Dr. V. Ilivitsky

Description of Study: The effectiveness of the nicotine skin patch in smoking cessation treatment has been well documented. The patch is believed to work because it delivers nicotine to brain and produces similar effects on mood and behavior as does smoking.

The objective of this study is to examine the effect of the nicotine patch on mood and on brain activity as measured by computerized EEG (electroencephalogram) techniques. You are participating in this study as an individual who uses cigarettes on a daily basis and experiences clear discomfort when attempting to quit the smoking habit.

Procedure: Three sessions are involved. During the first 'orientation' session, you will be introduced to the procedures that will be carried out in the subsequent two test sessions. In the two test sessions which begin at 8:00am, sensors will be placed on your scalp and around your eyes. The electrodes measure small amounts of electrical activity that your brain produces. You cannot feel the electrodes working and you cannot get a shock from them. You will then be asked to sit and relax with eyes closed for a brief period and rate your mood on a questionnaire. This procedure will be repeated at four hourly intervals following application of the skin patch. During one of your two test sessions, you will be administered a skin patch containing a standard treatment dose of 21mg of nicotine. In the other session you will be administered a placebo patch with no nicotine. The order of the administration will be random and you will not know what patch you are being administered. Test sessions will take place from 0800 to 1400 and you will have to abstain from cigarettes

Appendix F continued

and coffee the night before you arrive at the laboratory and also throughout the test sessions.

Possible Risks:

The risks are very slight. Brain wave activity monitoring procedures are similar to those carried out in regular general hospitals except these study procedures use computers for measurement. You may observe a mild temporary skin irritation where the EEG electrode contacts your skin. Abstaining from smoking may provoke psychological discomfort but this will be no more or less than what you have experienced when you try giving up the habit on your own. The risks associated with acute nicotine patch use are negligible compared to chronic tobacco use.

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Date

Signature of Research Subject

Date

Signature of Witness

END

1 9 - 1 1 - 9 6

FIN