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**Effects of Acute Haloperidol Administration on the
Smoking-Induced EEG/Mood Activation Response Profile**

Darlene Walker

1999

**A thesis submitted to the
Department of Psychology
in partial fulfillment of
the requirements for the degree of
Master of Science (Psychology)**

**Carleton University
Ottawa, Ontario, Canada**

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**“Effects of Acute Haloperidol Administration on the Smoking-induced EEG/mood
Activation Response Profile”**

submitted by

Darlene Walker

in Partial fulfillment of the requirements for
the degree of Master of Science

Chair

Thesis Supervisor

Carleton University
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ABSTRACT

Acute cigarette smoking induces self-reported arousal increments and a characteristic stimulant-like EEG response profile consisting of amplitude reductions in slow (delta, theta) wave frequencies and amplitude increases in fast (alpha, beta) wave frequencies. Given the dependence-producing nature of smoke-inhaled nicotine and the role of the dopaminergic system in drug dependencies, this study examined the role of dopamine in modulating the smoking-induced activation response. In a randomized, double-blind, repeated measures design, quantitative electroencephalographic (EEG) changes and self-reports induced by the smoking of a single cigarette were assessed following pretreatment with placebo and haloperidol (2 mg), a dopamine antagonist. Following placebo pretreatment, absolute (μV) and relative (%) amplitude slow frequency bands (delta, theta, α_1) were reduced and absolute (μV) and relative (%) amplitude fast frequency bands (α_2 , beta) were increased following cigarette smoking as compared to sham smoking. Haloperidol pretreatment inhibited the smoking-induced increase in absolute beta frequency. Self-ratings indicated that cigarette smoking induced increases in alertness, contentedness, calmness, and euphoria and reduced cigarette cravings as compared to the sham smoking condition. Smoking-related self-ratings were not altered by haloperidol, but subjects were less content overall in the haloperidol condition as compared to placebo. Discussion of these results focus on transmitter systems and their relationship to neuroelectric and behavioural activities associated with the smoking habit.

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Effects of Acute Haloperidol Administration on the Smoking-Induced EEG/Mood Activation Response Profile

Theories of Smoking Motivation

Why do people start smoking? Many of the factors are believed to be environmentally based, and include family, peer and cultural influences. Between 33 and 50 percent of people who experiment with cigarettes become regular smokers (Henningfield, Schuh & Jarvik, 1995). A majority of those who smoke have a large percentage of friends who smoke as compared to those who don't smoke (56% versus 14% respectively) (Ashton, 1983). While parental influence is also strong, the effect of siblings who smoke is even stronger. American teens believe that almost twice as many people smoke than the number that actually do (Ashton, 1983). Socioeconomic factors also play a role, in that less women appear to smoke in underdeveloped countries, while industrialized countries see an increase in female smokers.

Personality is also thought to have an influence on smoking behaviour. The differing personality types of smokers and nonsmokers are thought to precede the initiation of smoking (Ashton, 1983). Some characteristics believed to be inherent of the smoker type are risk-taking, impulsiveness, aggressiveness, earlier involvement in sexual relationships, use of alcohol and other drugs, and a preference for more social activities.

A great deal of controversy has been brought to the question of what maintains smoking behaviour. Two models of smoking behaviour, the addiction

and functional models, have been forwarded to account for the neuropsychobiological factors underlying smoking maintenance.

It has been difficult to ascertain a universal definition of 'addiction,' and the decision as to whether smoking falls into the 'addictive' category has also proven to be difficult. In previous years, cigarette smoking was first classified as a 'habit' which was thought not to be harmful. Then the omnibus term 'dependence' developed at the expense of addiction and habituation, which was defined in even more vague terms than its predecessors, causing a great deal of semantic confusion and difference in professional opinion (Gori, 1996). With the release of the Report of the U.S. Surgeon General (1988), nicotine was classified as an addicting drug, with severe health consequences. A definition of addiction has been given from various sources (American Psychiatric Association, 1994; U.S. DHHS, 1988); The Royal Society of Canada (1989) proposed that addictive behaviours be 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.

According to the addiction model, smoking fulfills these criteria. Evidence of an inverse relationship between the desire to cease smoking and actual behaviour has been given to support the addiction model (West, 1984). It has been suggested that it is the effects of withdrawal which keep smokers from abstaining

(Ashton & Golding, 1984; Henningfield, Schuh & Jarvik, 1995; West, 1984), a basic premise of the addiction model.

The regularity of smoking behaviour, the relationship of smoking with the rise and fall of blood nicotine levels, self-titration of nicotine intake from cigarettes of differing nicotine delivery and existence of withdrawal symptoms are all factors in favor of an addictive quality of nicotine (Stepney, 1996; Stolerman, 1990).

Depending on the situation, smokers adjust their smoking behaviour and nicotine intake, thereby allowing themselves to meet specific situational demands (Warburton, 1987). Even when given a cigarette which has a lower nicotine content than their usual brand, smokers will increase their cigarette consumption and smoke generation in order to receive the appropriate dosage (Warburton, Wesnes & Revell, 1984). This is a "finger-tip" control mechanism that smokers employ, which has also been referred to as the "nicotine titration effect (Russell, 1976)." Smoking pattern changes can be observed in various ways - through crude consumption of cigarettes, puff analysis, blood carboxyhemoglobin levels, weight of tobacco burned, butt analysis and blood and urinary nicotine levels (Russell, 1976). It appears that smokers try to achieve an average 10 ng/ml boost per cigarette in order to achieve the positive subjective and cognitive-behavioral effects (Russell, Stapleton & Feyerabend, 1995). In this review, it was indicated that nicotine regulation may not be as precise as once thought, as smokers are able to quickly adjust to a level of nicotine two-thirds their usual intake level, and smokers who switch to pipes or

cigars have blood nicotine and CO levels higher than ordinary cigarette smokers. Researchers have, however, found that in 50 to 60 percent of smokers, individual differences in blood nicotine levels are attributable to their smoking behaviour (Heming, Jones, Benowitz & Mines, 1983).

Smokers who are deprived of smoking also show performance decrements in cognitive tasks as compared to nonsmokers, which may be a result of a withdrawal response (West & Russell, 1985). Withdrawal from smoking can produce physiological and psychological effects similar to those seen from withdrawal of psychostimulants (Ashton & Golding, 1984).

Henningfield (1984) reported the commonalities between substances of abuse (such as opium and cocaine) and nicotine, and found a number of interesting similarities. These similarities included rapid development of continual use; experimentation usually leading to chronic use; relapse after cessation is usually highest in the first few months, which gradually tapers off; similar contexts and situations are present during relapse; tobacco abstinence symptoms resemble cocaine abstinence symptoms; and similar patterns of self-administration.

Others feel that this evidence is not sufficient enough to classify nicotine as an addicting substance (Robinson & Pritchard, 1995). Criticism of the addiction's model view of nicotine as an addictive substance is based primarily on the argument that smoking/nicotine use does not completely fulfill three primary criteria of addiction focused on in the U.S. Surgeon General's Report (1988), such that: 1) it is not a compulsive and controlled behaviour, 2) it does

not induce major psychoactive/intoxicating (euphoric) effects, and 3) it differs with respect to reinforcement of self-administration in comparison to other addicting drugs (Robinson & Pritchard, 1992). Similar arguments have been forthcoming from empirical studies which have contested the pervasiveness of the smoking withdrawal syndrome and the uniqueness of the reinforcing properties of nicotine for acutely abstaining smokers (Warburton, Revell & Walters, 1988). A problem with the addiction model is that it does not take into consideration that smoking has a number of other effects on smokers, psychological and behavioural, which are generally positive and rewarding to the individual, and may serve as a reinforcer to continue smoking. The functional approach to smoking motivation is based on the premise that smokers use cigarettes as a 'tool' or 'resource' that allows them to control their psychological state (Gilbert, 1994; Robinson & Pritchard, 1992; Stepney, 1979; Warburton, 1987; Warburton, Revell & Walters, 1988).

Smoking appears to have dose- and time-dependent biphasic mood effects in that it can act in a sedating manner, both calming and reducing anxiety or it can act as a stimulant in relieving feelings of boredom and increasing subjective alertness (Ashton, 1983). Smoking also has beneficial effects on cognitive processes in both smokers and nonsmokers, improving attention, learning, memory and information processing speed, and as such it is not similar to other addictive substances which have been typically shown to impair cognition (Warburton, 1992; Wesnes and Warburton, 1983). Many researchers also feel that certain aspects of smoking, such as taste, sensory responses in

the throat and upper airway, social aspects of smoking and behavioural manipulation of the cigarette are important aspects in the maintenance of smoking behaviour (Robinson and Pritchard, 1992; Rose et al., 1985; Rose, Behm & Levin, 1992).

Gilbert's (1994) review of motivational models of smoking behaviour criticized the Surgeon General's Report (1988) stating that "it does not account for important individual differences such as differences in types of smokers, psychopathology, personality and effects of stress (Gilbert, 1994)." Many factors have been proposed as motivators of smoking behaviour. Employing a questionnaire analysis of smoking attitudes and behaviours, McKennell (1970) identified seven factors: nervous irritation smoking, relaxation smoking, smoking alone, activity accompaniment, food substitution, social smoking and social confidence smoking. Social smoking was thought to increase in adolescence, then to decrease with age, while addiction was believed to be highest among those who smoked, both because of nervous irritation and for relaxation.

In summary, while the addiction model holds that people smoke in order to avoid withdrawal symptoms, it does not fully account for the reasons why all smokers smoke. The functional model also implements a behavioural and psychological factor into the equation, that people use cigarettes as a "tool" to provide much needed psychological and behavioural benefits, such as reduced anxiety and increased alertness and cognitive efficiency (Warburton, 1987). It may be best to assume that both approaches have qualities which may contribute to the purpose of smoking.

In contrast to the addiction model however, the functional approach has strongly emphasized the rational use of smoke-inhaled nicotine as a psychopharmacological tool for modulating brain systems, controlling arousal and mood states. Although empirical support for this stance has been forthcoming indirectly from cognitive performance studies which have evidenced increased subjective alertness as well as behavioral efficiency (i.e., improvements in speed and accuracy) in a range of psychomotor/vigilance/learning-memory tasks (Knott, et al., 1998a; Warburton, 1992; Wesnes & Warburton, 1983) following smoking/nicotine administration in smokers and nonsmokers, direct evidence of smoking/nicotine effects on human CNS arousal has for the most part been based on electroencephalographic (EEG) research (Domino, 1995).

EEG and Cortical Arousal

It is clear that brain-behavior relations are mediated by neural activity and these relationships have been vigorously pursued with EEG methodology over many decades as it is one of the few noninvasive functional windows on the brain. Changes in electrical activity reflect changes in the brain on at least two levels: (1) changes in the collective behavior of neurons, and (2) changes within the neuron, in cellular activity, metabolic or otherwise. The electrical signal detected by EEG is the final summation of a multitude of potentials generated by the cerebral cortex consisting of vertical columns of apical dendrites oriented towards the surface and axon projections to deeper structures (Fenton, 1989).

Action potentials of individual neurons are of very short duration with small localized current flow which is not summated over cells. Synaptic events, or more specifically, postsynaptic potentials (PSPs) resulting from depolarization or hyperpolarization of the postsynaptic membrane (depending on whether the synaptic activity was excitatory or inhibitory) produce a greater current flow and are associated with a wider membrane area. Thus, the signal detected by the scalp electrode is believed to be predominated by the synchronous summation of excitatory and inhibitory PSPs on dendrites and neuronal cell bodies, not the deeper axon action potentials (Goff, et. al., 1978; Goldensohn, 1979). Electrical activity of the superficial cortical layers is influenced by projections from the thalamus which in turn receive input from the brainstem ascending reticular activating system (ARAS) structures controlling sleep and wakefulness. Thus, during waking, the brisk tonic activity of ARAS leads to the desynchronization (low voltage, fast frequencies) of the cortical EEG while at sleep onset, the thalamocortical rhythms are unmasked and synchronized, leading to a slower, higher amplitude EEG signal (Andersen and Andersson, 1968; Fenton, 1989). The human EEG, although often rhythmic in nature, is generally of mixed frequencies from 0.1 to 1000 cycles per second (hertz: Hz), but meaningful frequencies in the human scalp EEG have an upper-frequency range of approximately 70 Hz (Niedermeyer, 1990; Rodin, et. al., 1971). This range is approximately subdivided into frequency bands defined as beta (Hz > 13), alpha (8-13 Hz), theta (4-7 Hz) and delta (Hz < 3). When the brain is at rest large areas of the cortex may fire in relative synchrony. Therefore, lower frequencies,

such as the alpha rhythm, are better detected than higher frequencies which are highly asynchronous and attenuated by transmission through the skull and scalp (Cooper, et. al., 1965). The EEG voltage (between 10-100 μ V) distribution of these frequency bands at the scalp results from the flow of current in a conductive medium usually referred to as volume conduction. The signal distributions are, however, also modified by the intervening tissue layers and the geometry of the cortical folding and are also dependent on the recording montage and the state of the subject at the time of recording.

Arousal theory involves the idea of a continuum of nervous activation ranging from deep sleep states to high emotional excitement states (Duffy, 1934) and although it is rightfully criticized today, the notion was seminal in proposing that emotional and motivational forces give rise to arousal changes which are somewhat independent from external events. Moruzzi and Magoun's (1949) discovery added strong impetus for the use of EEG as an indicator of central arousal as electrical stimulation of the mesencephalic reticular formation resulted in behavioral alerting and electrical changes like those following peripheral stimulation, and that these outlasted the stimulus. Moruzzi and Magoun's (1949) proposed general activation concept assumed a unitary control of the electrical activity of the cortex related to consciousness, arousal and the sleep-waking cycle by postulating that the nonspecific ascending reticular activating system was integral to the arousal response. Over the next four decades it was generally accepted that neocortical activation was mediated by the reticulothalamic projection system (Vanderwolf & Robinson, 1981). This

position has weakened as accumulated evidence has indicated that reticular nuclei projections to the cerebral cortex are nonexistent (Jones, 1985) and although they may play a significant role in neocortical rhythmic electrical synchronization they do not appear to be involved in activation-related electrical desynchronization (Steriade & Deschenes, 1984; Steriade et. al., 1985, 1997). Although thalamic (i.e., intralaminar nuclei) circuiting is required for electrocortical activation, it is well recognized that other subcortical structures including basal forebrain nuclei (Divac, 1975; Lehmann, et. al., 1980; Saper, 1984), dorsal raphe nuclei (Moore, et. al., 1978), the locus coeruleus nuclei (Lindvall, et. al., 1974) and ventromedial thalamic nuclei (Herkenham, 1979) may be involved in the activating process termed "arousal."

Early evidence of cholinergic involvement in cortical arousal was forthcoming from studies showing that systemic injection of the cholinolytic drug atropine abolished arousal-associated electrocerebral desynchronization (Wikler, 1952; Herz, 1959) an effect which was believed to be mediated via blockade of cholinergic neurons of the reticular formation terminating in the neocortex. Although the anatomical locus of cholinergic neurons responsible for electrocortical arousal is still not completely known and may involve cholinergic cells intrinsic to the cortex (Armstrong, et al., 1983; Houser, et al., 1985) or cholinergic projections from the brain stem to the thalamus (Hallanger, et al., 1987), the importance of the main cholinergic afferent system to the cortex, the basal forebrain (Divac, 1975; Jones, et al., 1976; Mesulam & Van Hoesen, 1976), has been underlined by the observations that nucleus basalis lesions,

using scopolamine, markedly decrease electrocerebral arousal as evidenced by dramatic increases in slow wave (delta and theta) activity and decreases in fast wave activity (beta) which was reversed by anticholinesterase treatment (Buzsaki, et al., 1988; Riekkinen, et al., 1991a; Riekkinen, et al., 1991b; Riekkinen, et al., 1991c). While this finding strongly supports a role for acetylcholine in neocortical EEG activation, it is recognized that separate frequency components of the EEG arousal response may be mediated by different transmitter systems (Steriade, et al., 1990).

Nicotine, EEG, and Animals

Nicotine is the main alkaloid in tobacco, and, aside from carbon monoxide, is the only known centrally active agent in cigarette smoke. Smoking appears to be an efficient route of nicotine administration for smokers which allows over 95 percent of the nicotine inhaled to be absorbed and pass to the brain in approximately 10 seconds (Revell, 1988; Russell, 1980). The nicotine contained in smoke is suspended on particles of tar small enough to enter tiny airways and lung alveoli. Nicotine readily crosses cell membranes due to its lipophilicity, absorbing into and affecting almost every system in the body. A single cigarette contains about 10 mg of nicotine, while the average intake from a cigarette is 1.0 mg, but may exceed this (possible up to 3 mg.). With a distribution half-life of 10 to 20 minutes and an elimination half-life of approximately two to three hours, blood nicotine levels increase throughout the day, reaching a plateau. During the night, this level decreases, resulting in low

blood nicotine levels in the morning. The daytime tolerance dissipates during the night, with the first few cigarettes of the day causing an increase in heart rate (Benowitz et. al., 1982). While five to 10 percent of nicotine is excreted by the kidneys, 80 to 90 percent is metabolized by the liver. Passive diffusion and active transport by the choroid plexus aid nicotine in crossing the blood brain barrier, and, by the use of autoradiographic techniques, has been found to be distributed throughout the brain, mainly in the hippocampus, hypothalamus, thalamus interpenduncular nucleus, superior colliculus, and areas of the cerebral cortex, predominantly layers III and IV (Arneric, Sullivan & Williams, 1995; Battig, 1980; LeHouezec & Benowitz, 1991).

At approximately body pH (7.36-7.44) nicotine is a positively charged ion, the nicotinium ion, which resembles acetylcholine (Ach) in spacing of positive and negative charges. Ach is a flexible molecule with both nicotinic and muscarinic receptors; muscarine, pilocarpine and arecoline are selective for the muscarinic receptor and nicotine is selective for the nicotinic receptor.

'Smoking doses' (5-40 $\mu\text{g/kg}$ i.v.) of nicotine administered to a number of animal species have consistently been found to induce electrocortical desynchrony and hippocampal theta activity (Clarke, 1990). A number of studies have focused on the CNS site and mechanism of action of nicotine in producing EEG activation. Although brain stem transection and electrolytic lesions of the mesencephalic reticular formation in cats prevented nicotine-induced desynchrony (Domino, 1967), it cannot be necessarily assumed that nicotine acted directly on these neurons. In a series of studies by Domino and

colleagues (Kawamura and Domino, 1969) administration of nicotine (up to 100 µg/kg) induced a marked EEG activation profile in caudal midbrain, but not rostral midbrain, transected cats which was effectively blocked by nicotinic (mecamylamine) and muscarinic (atropine) antagonists. In a more recent study nicotine (i.p.)-induced desynchronization in cats was antagonized by mecamylamine and by nucleus-basalis lesions (via quisqualic acid) but not by central (scopolamine) muscarinic or peripheral nicotinic (hexamethonium) cholinergic antagonists (Riekkinen, et al., 1993).

As cholinergic drugs may regulate EEG activity via receptors located in a number of brain regions including the cortex, the comparative electrocortical effects of nicotine were examined with respect to nucleus basalis and thalamic nuclei (Riekkinen, et al., 1995). The thalamic nuclei receive most of their cholinergic afferents from the brainstem pedunculo pontine and laterodorsotegmental cell groups and only the reticular and mediodorsal nucleus of the thalamus receive dual cholinergic projections from the nucleus basalis and brainstem cholinergic. Local microinfusions of nicotine (3, 10, 30 µg) or mecamylamine into the forebrain cholinergic neurons of the nucleus basalis failed to alter cortical EEG but nicotine microinfusions into the thalamus did alter EEG waves in the cortex, suggesting that nicotine may desynchronize EEG waves not via nucleus basalis nicotinic receptors but via brainstem cholinergic projections at the thalamus. The pedunculo pontine tegmental nucleus (PPTg) is believed to be one of the critical brainstem areas for cholinergic elicitation of rat hippocampal theta rhythm during high arousal behavioral states (Vertes, 1982;

Vertes, 1984 ; Vertes, et al., 1993; Webster and Jones, 1988). Nicotine, but not physostigmine, was found to reverse lesion-induced theta rhythm alterations (during exploratory sniffing) in cats in a dose-dependent manner and simultaneously induced cortical EEG desynchronization (Bringmann, 1997). Smoking doses of nicotine given to cats has also been found to induce electrocorticogram activation and acetylcholine release at the cortex while higher doses (80 µg/kg) decreased electrocortical arousal and acetylcholine release at the cortex (Armitage, et al., 1969). Although it is generally assumed that EEG effects of smoking in humans are most probably due to nicotine, in cats electrocortical desynchrony has been induced by tobacco smoke exposure and has been abolished by mecamylamine (Hall, 1970). It is quite probable that both nicotine and carbon monoxide contribute to the EEG effects of smoke inhalation as desynchrony was also observed in mecamylamine pretreated cats administered smoking doses of carbon monoxide.

Smoking, Nicotine and the Human EEG

Early research into the acute effects of smoking utilized 'novel' experimental cigarettes differing in nicotine/tar yield, from the smokers preferred cigarette brands. Typically, these produced desynchronized electrocortical patterns characterized by alpha diminution and beta augmentation, a pattern similar to that seen with intravenously administered nicotine (Church, 1989). That these electrical alterations were mediated specifically by nicotine was supported by the finding that nicotine-free cigarettes fail to produce any EEG

changes. Here, investigators examined the changes in heart rate and EEG when subjects were given two brands of cigarettes varying only in nicotine yield, one being an "ultra-low" cigarette with very little nicotine (0.06 mg.) and the other equivalent to a "light" brand cigarette in nicotine yield (0.60 mg.) (Robinson, Pritchard & Davis, 1992). The ultra-low nicotine cigarette produced a small percentage rise in heart rate in all subjects, but did not produce significant EEG changes. The "light" cigarette, however, produced changes which included an increased power in β_2 bands and a decreased power in delta bands. They concluded that tar and gas components contribute little to the CNS effects of cigarette smoke.

For the most part, these early studies extracted EEG profiles from one or two recording sites and, as studies with clinical psychotropics have observed pattern profiles differ across the scalp topography, smoking-EEG studies attempted to fine-tune their EEG response profiles with multi-lead scalp recordings. Investigating the effect of smoking on the topographic EEG of deprived heavy smokers, Domino, Riskalla, Zhang and Kim (1992) required subjects to smoke approximately three centimetres of either a sham cigarette, a nicotine-free cigarette (less than .05 mg) or a high (2.16 mg) nicotine cigarette. This study focused on alpha changes over the entire scalp that occurred as a result of smoking the high nicotine cigarette. A significant increase in heart rate was observed after smoking the high nicotine cigarette, but no significant changes were observed with sham smoking, and very little change with the nicotine-free cigarette. With respect to EEG, most significant changes were

observed with the high nicotine cigarette which induced significant increases in α_2 at most scalp sites. A second study by Domino and Matsuoka (1994) compared the topographic EEG patterns in volunteers after sham smoking and smoking each of three cigarettes of increasing nicotine yield (0.27, 2.0 and 2.16 mg, tar yield ranging from 25 mg. in low yield to 32 mg. in high yield). This study investigated changes in all frequencies, over the entire scalp. Alpha was found to change immediately after smoking, such that a mean decrease was observed in low frequency (8-10 Hz) α_1 power, and a mean increase was observed in high frequency (10-13 Hz) α_2 power across all scalp sites. As well, a small increase was observed during smoking in heart rate, systolic and diastolic blood pressure in comparison to sham smoking. There were no consistent changes observed in beta, delta or theta power. Similar topographic profiles of diffuse, widespread increments in α_2 power have been reported in later studies and have been associated with increases in subjective alertness, calmness, but not with ratings of euphoria (Knott, et al., 1995; Knott, 1998a) and are evident in smokers with average smoking histories of 9 and 52 years (Knott & Harr, 1996), suggesting that the EEG response is not subject to tolerance-related processes.

Topographic profiles induced by novel experimental cigarettes which differ from the smoker's preferred brand appear to result in a qualitatively different activation profile. When smokers were given experimental cigarettes with either low, medium or high tar/nicotine yields (Knott, 1989b), no significant EEG alterations were produced by the different cigarettes, but it was observed that relative to sham smoking (ie. the inhalation of non-lit cigarettes), smoking of

cigarettes with increasing tar/nicotine yield gave rise to a posterior-to-anterior spreading of relative power changes in the alpha and theta band frequencies. Theta reductions and alpha increments observed in the occipital/parietal region with low tar/nicotine yield cigarettes, progressed to the central, frontal and prefrontal sites with medium and high yield cigarettes, respectively.

In more recent years, experimenters utilizing period or Fast Fourier transform (FFT) power spectrum analyses of EEG signals have allowed subjects to smoke their preferred brand of cigarettes for the purpose of investigating the dynamic central changes that occur from cigarette smoking. One such study investigated the acute inhalation and puff-by-puff effects of smoking on EEG to see when EEG changes appear during the course of smoking a single cigarette, whether EEG is sensitive to the sequential stages of inhalation as well as the anticipatory period preceding puff inhalation, and to determine whether post-puff EEG activity follows the lung-to-brain transport time (approximately 10 seconds) of inhaled nicotine (Knott, 1988). After the eighth and final puff of cigarette smoking, significant effects were observed for three power bands, with delta and theta showing significant decreases and alpha showing significant increases, not decreases, relative to sham smoking. Beta activity showed no significant effects and an increase in peak alpha frequency (PAF) only approached significance. Significant EEG changes were observed at the fourth puff and were maintained through to the eighth puff. Slow (delta, theta) wave power reduction changes relative to sham smoking emerged 20-25 seconds following puff inhalation. In a similar study, the same EEG parameters for habitual low tar/nicotine smokers

smoking one of their preferred low tar/nicotine yield cigarettes were examined (Knott, 1989a). Overall, alpha power was found to increase, but not consistently until the sixth puff. Slow wave delta and theta were found to decrease, theta reductions appearing at puff five, and delta power reductions not occurring until the eighth puff. Significant increases in PAF did not occur with the low yield cigarettes.

Evidence that the smoking-induced EEG activation profile characterized by power shifts from slow (delta, theta) to fast (alpha₂, beta) frequencies is mediated by nicotine's central actions is in part supported by the observation that significant alpha₂ power increments are not observed until plasma nicotine levels reach a threshold level of 10.0–15.0 ng/ml (Domino, et al., 1995). Increasing plasma concentrations of nicotine produced progressively greater increases in beta power. Further, administration of nicotine via transdermal patch (21 mg) has been shown to result in identical EEG activation profiles with delta-theta power being reduced and alpha₂ and beta₂ power being increased at frontal, central and parietal sites, beginning one hour post-patch administration (Knott, 1997).

Attempts to examine the neurochemical basis of the smoking-induced EEG activation profile have been relatively scant and have for the most part focused on cholinergic transmission. In two of the three studies to date, acute mecamylamine (10 mg) pretreatment failed to block the smoking-induced suppression of slow (theta) wave power or the augmentation of fast (alpha) wave power (Knott, et al., 1995) but 20 mg did prevent the increase in mean alpha

frequency and alpha power induced by gum-delivered nicotine (Pickworth, et al., 1988). In the most recent study, based on the observation that nicotine-induced EEG activation was effectively blocked by atropine as well as by mecamlamine, Knott et al. (1998b) investigated the separate and combined effects of mecamlamine (20 mg) and scopolamine (0.6 mg) pretreatment on the proposed assumption that smoking-induced EEG activation may be caused by nicotine releasing acetylcholine onto muscarinic receptors (Clarke, 1990). The prototypical smoking-induced EEG activation was differentially affected by the separate and combined action of the cholinergic antagonists, with scopolamine proving to exert no antagonistic actions and mecamlamine, alone and in combination with scopolamine, tending to abolish slow (delta, theta) frequency (absolute power) reductions and fast (alpha₂, beta) frequency (relative power) increments. Self-ratings of smoking-induced increases in alertness were also attenuated by mecamlamine but not scopolamine administration. Failure of cholinergic antagonists to completely antagonize all components of the smoking-induced EEG activation profile suggest that the electrocortical response to smoking may be mediated by more than one transmitter system.

Smoking/Nicotine, Dopamine and EEG

As evidence has shown, acetylcholine plays a role in the activation response produced by smoking. However, many other transmitters are affected, directly or indirectly, upon administration of nicotine, which may act alone or in concert to produce behavioral and/or psychological effects. Other abusable

substances have been found to alter a range of neurotransmitters as well, in a greater proportion than cigarette smoking, and as such have been more extensively studied. Comparison of the results of these studies to those of cigarette smoking may help in forming an hypothesis about the neurochemical basis of the arousal/mood response and euphoria produced by smoking.

The characteristics of a number of substances of abuse is their ability to “enhance brain-stimulation reward or lower brain reward thresholds in the mesotelencephalic dopamine system (Gardner, 1997).” These substances generally enhance activity in reward-relevant brain circuits. The mesotelencephalic dopamine system is one of the two major dopamine systems in the brain, ascending from the ventral tegmental area (VTA A-10) to the limbic system, specifically the nucleus accumbens and amygdala. A component of this system runs through the medial forebrain bundle. The other major system is the nigrostriatal projection, ascending from the substantia nigra to the caudate nucleus and putamen, and is associated with voluntary control of movement (Joseph, Young & Gray, 1996).

In the mid-1960s, after many theories had been formulated about the areas responsible for the addictive qualities of these abusable drugs, with the help of new methods and advancing technology, sites positive for brain-stimulation reward and the mesolimbic dopamine system were found to highly correlate, with the major portions being carried through the medial forebrain bundle from the ventral mesencephalon to the limbic and cortical forebrain (Moore & Bloom, 1978). Therefore, the mesolimbic dopamine system appeared

to be a major contributor to brain-reward mechanisms. It has been shown that the crucial site for opiate electrical brain stimulation reward is the ventral tegmental area (Jenck, Gratton, & Wise, 1987), while the nucleus accumbens is crucial for the reward associated with amphetamine use (Colle & Wise, 1988).

In reviewing several brain microdialysis studies, which are studies done to determine the neurochemical mechanisms by which abusable substances enhance their rewarding effects, it appears that many of these drugs, including cocaine, amphetamine, morphine and other opiates, nicotine, alcohol, barbiturates and marijuana, all enhance extracellular dopamine levels in the neostriatum, and of particular importance, in the nucleus accumbens, by means of facilitating the release of dopamine, or inhibiting its reuptake (Gardner, 1997). These drugs increase extracellular dopamine mainly in the outer layer of the nucleus accumbens, suggesting this area is specialized for mediating brain reward functions. Single neuron electrophysiological techniques have found nicotine, within the range of 50-500 µg/kg administered intravenously, to induce activation of dopamine neurons in the mesolimbic region significantly more than in the mesostriatal area, an effect which was prevented or reversed by mecamylamine. This implicates that nicotinic cholinergic receptors may mediate this neural activation (Mereu, et al., 1987).

This dopamine link, however, is thought to be the "second stage" crucial step in the brain reward system. The pathway of activation of these reward mechanisms, as reviewed by Gardner (1997), is thought to start in the "first-stage" neurons originating in the anterior nuclei of the medial forebrain bundle,

which project caudally in a fast-conducting, myelinated neural network of unknown transmitter type. These neurons send their message to the dopamine neurons of the ventral tegmental area ("second-stage"), an area heavily innervated and modulated by other neurotransmitter systems. These dopaminergic neurons project rostrally to synapse on the nucleus accumbens, another significantly innervated area modulated by other systems, being the "third stage" reward relevant neurons which carry the signal a little further. Within this framework, the ventral tegmental area and the nucleus accumbens appear to be the most important dopaminergic link for drug-induced changes in hedonic tone (Gardner, 1997).

Several animal studies have been performed investigating the involvement of the dopamine system in the effects of nicotine. Because nicotine produces similar (although less powerful) psychostimulant effects as d-amphetamine and cocaine, drugs which appear to increase extracellular dopamine in the mesolimbic system in rats, and also produce "conditioned place-preference", a result in which an animal tends to return to a place that was previously associated with a particular drug, it was hypothesized that nicotine is also affecting this dopamine system (Clarke, 1991). The most rewarding administration of d-amphetamine or cocaine produced was intracerebral injection to the nucleus accumbens, while injections to other areas do not appear to affect the psychostimulant effect or conditioned place-preference (Clarke et al, 1990). However, dopamine receptor blockade reduced these effects. Acute administration of nicotine increased the neurotransmitter activity in the

mesolimbic system, suggestive of increased dopamine activity within this system (Clarke, 1991).

The effects of acute nicotine appear to produce a significant increase of dopamine in the nucleus accumbens (up to 49 percent) and anteromedial striatum (up to 37 percent), while repeated injections reduced these effects in lab rats (Vezina, et al., 1991). An opposite effect to this occurred in the medial prefrontal cortex. However, morphine, in comparison, increased dopamine in the nucleus accumbens and medial prefrontal cortex, with repeated injections enhancing effects in the nucleus accumbens and reducing effects in the medial prefrontal cortex. This suggests that nicotine mediates the effects produced by dopamine in a different way than morphine. Self-administration of nicotine was reduced following administration of selective D₁ and D₂ dopamine receptor antagonists; these same antagonists produced a compensatory increase in cocaine self-administration within the same range of dosage (Corrigall, 1991). A review of studies using one of three procedures (in vivo microdialysis, 6-hydroxydopamine lesions of the nucleus accumbens or operant avoidance conditioning), found that pretreatment with nicotine enhanced the nucleus accumbens' release of dopamine, an effect which corresponds with an increased locomotor response (Balfour, Benwell & Vale, 1991). Many of the earlier studies performed on animals to investigate the activity of dopamine produced by administration of nicotine gave high doses of nicotine to animals, surpassing the normal intake of a regular smoker (Benwell, 1990). A number of these latter studies focused on the locomotor activity of the rat, finding that locomotor activity

was increased after large doses of nicotine, similar to other psychostimulants. However, the large doses may not be producing the results that we would find with lower, more natural doses. It was thought that the mesolimbic system was involved in the locomotor activity produced by nicotine; as such, pretreatment with nicotine produced secretion of dopamine from the nucleus accumbens with a challenge dose. This increase, however, was modest in comparison to the dopamine increase produced by other psychostimulants.

In recent years, the involvement of dopamine in the electrophysiologic effects produced by nicotine has been investigated in animals, with particular emphasis on the D₁ dopamine receptors. Activation of D₁ dopamine receptors causes desynchronization of all frequency bands and a decrease in power, while D₂ receptor activation selectively increases the alpha₁ band (Ferber & Kuschinsky, 1994). In investigating whether activation of D₁ receptors occurred after ingestion of nicotine, rats were administered nicotine, SCH23390 (a D₁ dopamine receptor blocker) or prazosine (an alpha₁ adrenoreceptor blocker) alone or in combination. Nicotine (0.2 mg/kg) decreased power in all frequency bands except beta₂, and produced desynchronization of the EEG. SCH23390 alone (subcutaneous injection of 1 mg/kg) increased activity in the first 30 minutes after administration, significance occurring only in the alpha₂ frequency band. The decreases produced by nicotine alone were similar to that produced by nicotine and SCH23390, such that it appeared that SCH23390 did not have an effect on nicotine. Prazosine produced increases in a number of frequency bands with the exception of delta and beta₂, although again, like SCH23390, it

did not block the power-reducing effects of nicotine. Therefore D₁ dopamine receptors and alpha₁ adrenoreceptors were, it was concluded, not involved in the neuroelectric effects of nicotine (Ferber & Kuschinsky, 1994).

That dopamine plays a minor role in the EEG effects of nicotine was suggested by these same researchers a few years later (Ferber & Kuschinsky, 1997), using a larger dose of nicotine. Nicotine (0.4 mg/kg subcutaneous injection) was administered to rats while extracellular dopamine in the striatum was estimated. This produced a decrease in all frequency bands except beta₂ for a duration of longer than 60 minutes, and significantly increased extracellular dopamine in the striatum up to 130 percent.

While these animal studies are not definitive, they are suggestive of a dopaminergic component in the rewarding effects produced by nicotine, and they appear to be supported by behavioural studies with dopaminergic antagonists.

In an investigation of electrical self-stimulation in the VTA following administration of nicotine, animals were pretreated with acute injections of haloperidol (0.03 mg/kg⁻¹ subcutaneous (s.c.) injection), mecamylamine (1.0 mg/kg⁻¹ s.c.), scopolamine (3.0 mg/kg⁻¹ s.c.) or ondansetron (0.01 and 0.1 mg/kg⁻¹ s.c.) (Ivanova & Greenshaw, 1997). Daily administration of nicotine (0.6 mg/kg⁻¹) produced a decrease in thresholds and an increase in responding for reward (self-stimulation). Mecamylamine and haloperidol both diminished the effects of nicotine on self-stimulation, while having no effect on the control group; neither scopolamine nor ondansetron had any effect on nicotine-induced responding.

Selective D1 and D2 dopamine antagonists have been used to examine nicotine self-administration, food-maintained responding as well as locomotor activity (Corrigall and Coen, 1991). All three antagonists used in this study (SCH23390, Spiperone and haloperidol, all delivered s.c. in a 1 mg/kg dose) resulted in a decrease in the number of nicotine infusions the animals obtained, but did not render them unable to respond, as they initially responded the same way they had before administration of the dopamine antagonists.

To date, only one study has investigated the effects of dopamine antagonist action with respect to smoking-related subjective feelings and behaviours (Dawe, Gerada, Russell & Gray, 1995). Following administration of an acute D₂ antagonist (5 mg. haloperidol), smokers increased their cigarette consumption significantly in comparison to those who received placebo pretreatment. No difference was found on subjective measures between haloperidol and placebo groups. The results of this study were thought to portray a compensatory increase in nicotine in order to receive the reward associated with smoking and, as such, to bypass negative withdrawal symptoms associated with low central concentrations of functional nicotine.

Objectives

The primary purpose of this study is to investigate changes in EEG produced by smoking when subjects are pretreated with the dopamine antagonist, haloperidol. As smoking-induced EEG activation is frequently associated with mood alterations, the assessment will include self-ratings of

mood and euphoria as well as ratings of cigarette acceptability and cigarette craving.

Hypothesis 1: Compared to sham smoking, cigarette smoking following placebo pretreatment will induce an EEG activation profile involving increased amplitudes in high (alpha, beta) and reduced amplitudes in low (delta, theta) frequency bands.

Hypothesis 2: Compared to sham smoking, cigarette smoking following placebo pretreatment will induce subjective activation, i.e. alertness.

Hypothesis 3: Compared to sham smoking, cigarette smoking following placebo pretreatment will induce decreases in craving, increases in euphoria and cigarette acceptability ratings.

Hypothesis 4: Compared to placebo, haloperidol pretreatment will inhibit EEG activation normally produced by cigarette smoking.

Hypothesis 5: Compared to placebo, haloperidol pretreatment will inhibit subjective mood activation.

Hypothesis 6: Compared to placebo, haloperidol pretreatment will inhibit the craving reductions and subjective euphoric effects produced by cigarette smoking.

METHOD

Experimental Subjects

Sixteen paid subjects were used for this study. Subjects were recruited through a newspaper ad and posters at a university. All subjects were male, right-handed, mean age of 27.5 years (SD=9.23). The average number of cigarettes smoked per day was 22.19 (SD=5.58) and number of years smoking was 11.59 (SD=9.34). The mean nicotine level of the cigarettes smoked by the subjects was 1.08 mg. (SD=.19), mean tar level was 11.19 mg (SD=2.99) and mean CO level was 11.31 mg (SD=3.14). All subjects fulfilled telephone interview criteria involving questions on smoking, alcohol and drug history, medication use and physical/neurological illness, and passed a short medical exam. Subjects were screened on the basis of several inclusion and exclusion criteria:

(i) Inclusion criteria were:

1. male;
2. right-handed;
3. 20 to 49 years of age;

- 4. current smoking history of five or more consecutive years;**
- 5. presently smoking, with reported inhalation, a minimum of 15 cigarettes per day with cigarettes containing nicotine yields of at least 0.5 mg.;**
- 6. medical history and physical examination;**
- 7. judged to be reliable in study requirements;**
- 8. voluntary participation as per consent form (see Appendix A).**

Medical history and a medical exam were taken to ensure results would not be confounded with physical disorders which may disrupt drug metabolism and/or drug absorption and kinetics, and that no CNS disorders would confound the EEG signal.

(ii) Exclusion criteria were:

- 1. present or past psychiatric history (according to DSM-IV criteria) including alcohol/drug abuse;**
- 2. use of prescription and non-prescription medications that may significantly affect CNS functions and/or interact with nicotine or haloperidol administration;**
- 3. history of allergic reactions;**
- 4. a past history of Parkinson's disease or other neurological disorders;**
- 5. any other serious medical condition.**

Study Design

Subjects attended the laboratory for one orientation session, and two morning testing sessions, in which they received either a placebo, or a single dose of haloperidol (2 mg) within a repeated measures, randomized double blind design. Session order was counterbalanced according to Latin Squares procedures and each testing session was approximately one week apart. In each of the two study sessions, measures were collected prior to drug treatment, and again preceding and following sham smoking and following cigarette smoking.

Study Procedure

Recording sessions were carried out in the morning (8:00 a.m. - 1:00p.m.) Subjects were required to abstain from smoking, alcohol, and CNS-acting drugs for 12 hours (overnight) prior to morning sessions. Each session followed an identical time table (see Table 1).

Insert Table 1 about here

Upon arrival to the laboratory, EEG hook-up was initiated, followed by a pre-drug EEG recording, and completion of self-rating mood, craving and euphoria scales. Administration of the drug (2 mg. haloperidol) followed, with a 120 minute drug absorption period during which subjects were allowed to read or view a selection of emotionally neutral videos. At approximately 140 minutes

Table 1**Test Session Time Schedule**

Time	Procedure
0800	Arrival time
0800-0830	EEG hookup
0830-0900	Baseline testing
0900-0905	Drug administration
0905 –1105	Drug absorption period
1105-1125	Pre-sham smoking recording
1125-1130	Sham smoking
1130-1150	Post-sham smoking recording
1150-1200	Cigarette smoking
1200-1220	Post-cigarette smoking recording
1220-1225	Removal of cap and electrodes

subjects sham smoked a single cigarette and at approximately 160 minutes they smoked one of their own cigarettes. Measures collected in the pre-drug test battery were acquired again immediately before and after sham smoking and then after cigarette smoking. In addition to the mood, euphoria and craving ratings, subjects completed a brief analogue scale questionnaire on sensory/taste aspects of smoking after the cigarette smoking period.

Drug Administration

Haloperidol (2 mg.) was administered in an orange juice solution, identical to the placebo.

Sham/Cigarette Smoking

Sham smoking involved the subject having 10 puff inhalations (1 puff per 30 sec) of a non-lit cigarette while cigarette smoking required the subject to smoke a lit cigarette from their preferred brand in the same manner until completion.

Self-Rating Questionnaires

Mood was assessed using the Bond and Lader self-report scale which consists of 16 bipolar analogue scales of various mood dimensions (see Appendix B) that, when analyzed and grouped, results in 3 mood factors: contentedness (average of 5 items), alertness (average of 9 items) and calmness (average of 2 items). Previous research has shown this instrument to

be sensitive to acute and chronic administration of a wide variety of psychotropics (Bond & Lader, 1974).

A euphoria questionnaire (the Morphine-Benzedrine Group (MBG) from the Addiction Research Center Inventory (ARCI); Haertzen & Hickey, 1987) was also administered following each of the EEG acquisitions, consisting of 17 true-false questions (see Appendix C). The number of true responses given was added up and this was the euphoria score given at each time.

A third questionnaire was administered following the recording of each EEG profile that asked about craving. This consists of 6 bipolar analogue rating scales, one scale measure of general cigarette craving and five measures of cigarette craving for specific functional objectives (see Appendix D). Each question was examined individually in the analysis.

Cigarette Ratings

The cigarette appraisal questionnaire was administered following smoking of the real lighted cigarette. It utilizes bipolar analogue scales to examine 'sensory' aspects of smoke inhalation as well as general liking of the cigarette (Knott, et al., 1998b)(see Appendix E).

EEG Acquisition

Recordings were carried out in a sound-attenuated chamber immediately adjacent to the control room housing the computer, video monitors, amplifiers and recorders. During recording sessions, subjects sat in a semi-reclined

position, with eyes closed, legs elevated and neck and arms supported for a six minute vigilance-controlled EEG acquisition period. Subjects were alerted during any signs of behavioral drowsiness.

Tin electrodes were positioned on 9 scalp sites according to the International 10/20 system (Fz, F3, F4, Cz, C3, C4, Pz, O1, O2) and were referenced to electronically-linked earlobes. An additional electrode placed between Fp1 and Fp2 served as a ground and all electrode impedances were kept below 5 KOhms. Electro-oculographic (EOG) activity was recorded from electrodes positioned on the right supraorbital ridge and right orbital canthus referenced to the mid-frontal site. In order to reduce frequency and extent of EOG and non-cerebral artifact, subjects were informed prior to each recording of the possible contaminating effects of eye movements, muscular contractions and gross motor movements of EEG activity. Electrical signals were recorded with an amplifier bandpass setting of 0.5 to 70.0 Hz. Continuous analog-to-digital samples (200 Hz) for each of the 10 channels were stored on optical disk for later off-line analysis.

EEG Quantification

During off-line analysis of pre- and post-drug EEG recordings digitized data points from a minimum of thirty 2 sec. duration artifact-free epochs (not associated with muscle activity, body movements, EOG deviations) were subjected to a Fast Fourier transform (FFT) analysis for calculation of average absolute (μ V) and relative (%) amplitude in five EEG frequency bands - delta

(δ :1.5-3.5 Hz); theta (θ : 3.5-7.5 Hz); alpha₁ (α_1 :7.5-10.0 Hz); alpha₂ (α_2 :10.0-12.5 Hz); and beta (β :12.5-25.0 Hz). Relative amplitude (%) was calculated by expressing amplitude in each band as a percent of amplitude in the total frequency spectrum (1.5-25.0 Hz).

Analysis of findings

Absolute amplitude, relative amplitude and frequency indices for each EEG band were subjected to separate 2 (drug) x 2 (smoking) x 9 (site) univariate repeated measures analysis of variance (ANOVA) procedures using 'difference score' measures whereby pre-drug (baseline) values were subtracted from post-sham smoking and post-cigarette smoking values to yield 'net effects' for both smoking conditions in each drug session. In order to keep the number of statistical tests to a minimum, significant site effects were only followed up if they interacted with smoking and/or drug effects. Drug and smoking effects were followed up if they were significant on their own or if they interacted with each other or an electrode recording site factor. The conservative Greenhouse-Geiser probability values were used where appropriate in order to reduce the occurrence of Type I errors associated with multiple tests and repeated measures.

Difference scores (sham and cigarette smoking minus baseline) for mood ratings (alertness, contentedness and calmness, each assessed individually) extracted from the 2 drug conditions were analyzed with separate 2 (drug) x 2 (smoking) ANOVAs. Difference scores for euphoria were calculated for the

sham and smoke conditions in the same manner and were compared again using 2(drug condition) x 2(smoke condition) ANOVAs. Analysis of the craving self-ratings was the same as for both mood and euphoria, although each question was assessed individually. Raw scores for sensory/liking ratings following smoking a real cigarette during both placebo and haloperidol conditions were analyzed using one-way ANOVAs. Significant main or interaction effects for all ANOVAs were followed up using t-tests.

An analysis of the relationship between smoking-induced EEG alterations and smoking-induced mood, craving euphoria and sensory/liking questionnaire results was performed using the Pearson correlation coefficient. In order to reduce the number of statistical tests, correlations were only carried out on significant smoking-induced alterations; for EEG, values were averaged across significant sites, thus reducing each EEG index (e.g. absolute alpha amplitude) to a single value.

RESULTS

(1) EEG

(i) Absolute:

Absolute amplitude difference scores induced by sham and real smoking during placebo and haloperidol conditions are shown in figure 1. Significant main effects were found for drug condition at delta ($F(1,15)=12.93$, $p=.003$) and beta ($F(1,15)=6.89$, $p=.02$). Delta was reduced in the placebo group and increased in the haloperidol group, while beta increased in the placebo condition

more than the haloperidol condition. Significant effects were observed for smoking condition at delta ($F(1,15)=28.71$, $p=.0001$), theta ($F(1,15)=11.10$, $p=.005$) and beta ($F(1,15)=10.48$, $p=.006$). While delta and theta increased in the sham condition and decreased in the smoke condition, beta increased more during real smoking than during sham smoking.

Insert Figure 1 about here

Follow-up analysis of a significant smoke by site interaction observed at α_2 ($F(8,120)=5.50$, $p<.0001$) revealed that α_2 was reduced during sham smoking and increased during real smoking at F_2 ($t(15)=-2.26$, $p=.04$), O_1 ($t(15)=-2.69$, $p=.02$), and O_2 ($t(15)=-2.61$, $p=.02$). At absolute beta, a significant interaction between drug and smoking conditions ($F(1,15)=4.99$, $p=.04$) revealed a significant difference between sham and real smoking in the placebo condition, such that smoking increased beta more than sham ($t(15)=-3.83$, $p=.002$). These same effects were not found during the drug condition. A significant difference between placebo and haloperidol at the real smoking condition such that beta increased in the placebo condition more than the haloperidol condition while subjects were really smoking ($t(15)=3.09$, $p=.008$).

(ii) Relative:

Relative amplitude difference scores induced by sham and real smoking during placebo and haloperidol conditions are shown in figure 2. Analysis of relative

Figure 1. Mean ($\pm$ SE) change (Δ) in log-transformed absolute power induced by sham and cigarette smoking following placebo and haloperidol. Values are averaged across electrode sites.

amplitude difference values showed significant drug effects for delta ($F(1,15)=7.56$, $p=.014$) and beta ($F(1,15)=8.47$, $p=.011$) such that delta was reduced for the placebo group and increased for the haloperidol group while beta exhibited the opposite effect of an increase in the placebo group, and decrease in the haloperidol group. A significant effect for smoking condition was also observed for delta ($F(1,15)=7.32$, $p=.016$), theta ($F(1,15)=12.72$, $p=.003$), α_2 ($F(1,15)=9.77$, $p=.007$) and beta ($F(1,15)=28.74$, $p=.0001$). Delta and theta were found to increased in the sham condition while being reduced in the real smoking condition, and α_2 and beta exhibited the opposite effect of decreasing during the sham condition and increasing during real smoking.

Insert Figure 2 about here

Several interactions were also observed to be significant, between the smoking condition and EEG site, at delta ($F(8, 120)=3.57$, $p=.001$), α_1 ($F(8,120)=4.14$, $p=.0002$) and α_2 ($F(8,120)=7.16$, $p<.0001$). Follow up analyses of delta revealed a significant difference between sham and real smoking difference scores such that delta increased in the sham condition and decreased in the real smoking condition at F_3 ($t(15)=2.74$, $p=.015$), F_4 ($t(15)=2.54$, $p=.023$), F_z ($t(15)=2.82$, $p=.013$), C_3 ($t(15)=2.50$, $p=.025$), C_4 ($t(15)=2.29$, $p=.037$), C_z ($t(15)=2.78$, $p=.014$), O_1 ($t(15)=3.21$, $p=.006$) and O_2 ($t(15)=3.02$, $p=.009$). α_1 was found to decrease significantly more during the real smoking condition than the sham condition at P_z ($t(15)=2.38$, $p=.031$). Sham

Figure 2. Mean ($\pm$ SE) change (Δ) in log-transformed relative power induced by sham and cigarette smoking following placebo and haloperidol. Values are averaged across electrode sites.

smoking was found to reduce α_2 while real smoking was found to increase it at all sites (F_3 ($t(15)=-3.11$, $p=.007$), F_4 ($t(15)=-3.08$, $p=.008$), F_z ($t(15)=-3.20$, $p=.006$), C_3 ($t(15)=-2.54$, $p=.023$), C_4 ($t(15)=-2.61$, $p=.02$), C_z ($t(15)=-2.62$, $p=.019$), P_z ($t(15)=-2.47$, $p=.026$), O_1 ($t(15)=-3.72$, $p=.002$) and O_2 ($t(15)=-3.59$, $p=.003$)).

(2) Questionnaires:

(i) Mood:

Mood change scores induced by sham and real smoking during placebo and haloperidol conditions are shown in figure 3. Analysis of alertness yielded a significant difference between sham smoking and real smoking conditions ($F(1,13)=9.02$, $p=.010$), such that ratings of alertness were higher in the real smoking condition than in the sham condition. Another significant difference was observed between the smoking conditions with respect to contentedness ($F(1,13)=11.08$, $p=.005$). The real smoking condition also reported more contentedness than the sham smoking condition. Subjects also reported feeling more calm following real smoking as compared to sham smoking ($F(1,15)=12.84$, $p=.003$). The drug conditions were found to be significantly different with respect to contentedness as well ($F(1,13)=6.21$, $p=.027$), such that overall subjects were more content during the placebo condition than the haloperidol condition. No other significant differences were observed.

Insert Figure 3 about here

(ii) Craving:

Craving change scores induced by sham and real smoking during placebo and haloperidol conditions are shown in figure 4. Significant results show a difference between the sham and real smoking conditions for craving overall ($F(1,15)=15.67$, $p=.001$), craving related to anxiety ($F(1,15)=10.92$, $p=.005$), craving related to drowsiness ($F(1,15)=11.81$, $p=.004$), craving related to irritability ($F(1,15)=10.61$, $p=.005$) and craving related to feeling unfocused ($F(1,15)=9.36$, $p=.008$). No other significant results were found. On observing the means for each question, it was found that subjects had a higher craving score for the sham condition than the smoking condition for each of the questions.

Insert Figure 4 about here

(iii) Euphoria:

Euphoria change scores induced by sham and real smoking during placebo and haloperidol conditions are shown in figure 5.

Figure 3. Mean ($\pm$ SE) change (Δ) in mood ratings for alertness, contentedness and calmness following sham and cigarette smoking for placebo and haloperidol conditions.

Figure 4. Mean ($\pm$ SE) change (Δ) in craving following sham and cigarette smoking for placebo and haloperidol conditions.

Insert Figure 5 about here

A significant result was found in the smoking condition ($F(1,15)=5.68$, $p=.031$) such that on comparison of the means, while smoking did not increase euphoria, sham smoking decreased euphoria. No other significant results were found.

(iv) Appraisal:

Appraisal scores of cigarettes during real smoking for placebo and haloperidol conditions are shown in figure 6. No significant results were found. Therefore, no difference was observed in the characteristics of the cigarette from the placebo or haloperidol groups. A final appraisal question asked whether there was a change in the characteristics while the subject was smoking the cigarette. Two subjects answered that there was a marked change in the characteristics, one subject responding during the placebo condition, and one during the haloperidol condition.

Insert Figure 6 about here

Figure 5. Mean ($\pm$ SE) change (Δ) in euphoria ratings following sham and cigarette smoking for placebo and haloperidol conditions.

Figure 6. Mean scores ($\pm$ SE) of sensory/taste appraisal ratings for cigarettes following placebo and haloperidol conditions.

(3) EEG - Questionnaire Correlations

Of the correlations carried out between significant smoking-induced EEG indices and significant cigarette smoking-induced questionnaire responses, only a few showed significant results. The significant results for absolute and relative amplitude can be seen in table 2.

Insert Table 2 about here

Alertness was found to increase with increased change in absolute ($r=.512$, $p=.042$) and relative ($r=.534$, $p=.033$) α_2 following smoking. As change in relative beta increased following smoking, calmness was also reported to increase ($r=.554$, $p=.026$). Finally, as changes in α_2 related to smoking increased, euphoria was reported to decrease ($r=-.672$, $p=.004$).

Table 2

Absolute and Relative Amplitude EEG and Questionnaire Significant**Correlations**

	alertness	Calmness	euphoria
Absolute alpha₂	r=.512 p=.042		
Relative alpha₂	r=.534 p=.033		r=-.672 p=.004
Relative beta		r=.554 p=.026	

DISCUSSION

The purpose of this study was to investigate the role that dopamine plays in the production of the smoking-induced EEG activation profile, and its role in the reward mechanisms associated with smoking. The interpretations of the neuroelectric/behavioural profiles induced by smoking and the modulation of these profiles with acute dopaminergic antagonist treatment depends to a great extent on the experimental paradigm from which these observations are drawn. The present study design/procedure was clearly lacking on several fronts.

First of all, the order associated with sham and real smoking conditions could not be randomized or counterbalanced. This is because effects associated with cigarette smoking could be carried over to the sham smoking effects, which would result in incorrect data. Therefore, it was necessary for sham smoking to precede real smoking.

Second, administering a single dose of haloperidol, not allowing for time- and dose dependent response measures to be taken, and not monitoring absorption of the drug prevented the documentation of the complete pharmacokinetic/pharmacodynamic profile of nicotine and dopamine manipulations. These are areas that should be investigated in future research, as a single study may not be able to investigate this with accuracy. This study is considered a step in a multitude of investigations that have yet to be performed.

Third, the sample size was relatively small in this study. As well, females were excluded. No measure was taken to delineate heavy smokers from light smokers other than number of cigarettes smoked per day, number of

years smoking, and depth of inhalation. However, the protocol of this study was set up to reduce variation, and provide for consistency, and statistical power was found to be sufficient with 16 subjects.

In addition, subjects were allowed to smoke their preferred cigarette brand, therefore not standardizing the nicotine/CO/tar levels associated with smoking. However, different results have been found with the use of standardized cigarettes, and use of the subjects preferred cigarette provides for a more natural CNS exposure to nicotine with little chance of over- and under-dosing with nicotine. Also the use of a sham smoking condition was not an ideal placebo, as the conditioned response associated with sham smoking with respect to the behavioural and psychological aspects may have affected the results (Mucha, Pauli and Angrilli, 1998). However, use of ultra low nicotine cigarettes as a possible option may have been compromised by the subjects novel/arousal response to these typically 'unacceptable' cigarettes.

Subjects were also asked to refrain from smoking after midnight the night prior to the testing session. No control mechanism was implemented to ensure that this was the case. However, previous studies testing carbon monoxide levels to assess subject compliance have found compliance to be extremely high. Subjects were reminded by telephone the night prior to the test session of the importance of refraining from smoking. The deprivation period was implemented to ensure that any daytime tolerance to smoking had not occurred, and to guarantee the EEG activation profile associated with smoking would not be affected by anything other than experimental manipulation. As such, the

findings following this acute deprivation may be unique, and not easily generalizable to other situations.

The dose of haloperidol given to subjects was low (2 mg.). The purpose of giving a small dose was to reduce the possibility of sedation interfering with the neuroelectric measures taken. Only one significant subjective effect was observed between the haloperidol and placebo conditions for contentedness. While the haloperidol dose was lower than other studies, binding affinity for D₂ dopamine receptors has been shown to be very high – 64-82% D₂ receptor occupancy has been obtained by classical antipsychotic drugs, such as haloperidol (Farde, et al., 1992; Meltzer and Stockmeier, 1992; Nyberg, Farde, and Halldin, 1997).

Finally, the current study was limited to EEG and questionnaires. Future research may entail the use of a performance task to analyze the effect of haloperidol on reaction time following cigarette smoking. While nicotine is reported to improve performance on various tasks, including reduction of reaction time in both smokers and nonsmokers (Knott, Harr, Ilivitsky and Mahoney, 1998b), haloperidol has been shown to increase reaction time in normal volunteers (Diekmann, Grozinger, Westphal, Reinke and Kornhuber, 1996), while addition of an anticholinergic drug returned the response to a normal level.

Despite these cautionary restrictions, the derived study observations provide some preliminary insight into the pharmacologic and physiologic basis of the cigarette smoking habit which may be useful in constructing testable

hypotheses regarding the relevance of brain electric changes to motivational issues involved in smoking initiation and maintenance.

The present study was congruent with previous EEG investigations of acute cigarette smoking, the effects of smoking a single cigarette producing amplitude reductions in slow frequencies (absolute and relative delta, theta and α_1) and amplitude increases in fast frequencies (absolute and relative α_2 and beta). Haloperidol produced increases in absolute and relative delta, theta and α_1 frequencies, while producing decreases in α_2 and beta as compared to placebo. These results are in keeping with previous investigations of haloperidol's acute effects on the EEG spectrum of normal subjects, showing increases in slow wave activity, a variable effect for alpha activity, and reduction in fast wave activity (Wieneke, et. al., 1981).

Smoking-induced amplitude increments in absolute beta were significantly altered with the use of haloperidol, reducing beta amplitude increments observed during the placebo condition. The modulation of smoking-induced incrementation via dopamine blockade is quite distinct from the previously reported effects of nicotinic blockade which was found to prevent the smoking-induced absolute amplitude decreases in slow (delta, theta) frequencies but did not alter smoking-induced fast (α , beta) frequency absolute amplitude increases (Knott, et al., 1998b).

Absolute α_2 reductions occurred only at frontal and occipital sites while relative α_2 reductions were observed over all sites during sham as compared to real smoking. Relative delta was also found reduced at most sites

following sham smoking as compared to real smoking. Relative α_1 only decreased significantly in the parietal site.

These results taken all together support the objective that haloperidol pretreatment significantly inhibits a specific band component of the EEG activation profile produced by acute cigarette smoking.

Observations of mood produced results that coincided with previous reports of parallel findings for the smoking-induced neuroelectric activation profile and self-ratings of mood (Knott, et al., 1998b). Alertness was found to increase following real smoking, as did contentedness and calmness, regardless of drug condition, as compared to sham smoking, indicating different neurochemical pathways modulating smoking-induced physiologic and mood activational responses. A previous report indicated that smoking-induced alertness increments were significantly blocked by combined nicotinic/muscarinic (i.e. via mecamylamine and scopolamine) pretreatment but not by nicotinic or muscarinic blockade alone (Knott, et al., 1998b). However, the feeling of contentedness reported by subjects differed for the placebo and haloperidol conditions. Subjects in the placebo condition felt more content, while those in the haloperidol condition felt less content overall. Although no adverse side effects were experienced with acute dosing, the haloperidol-induced subjective drowsiness which typically accompanies the drug and/or the dopaminergic blockade in the nigrostriatal and mesotelencephalic pathways may have generally exacerbated any smoking-deprived related distress the subjects may have been experiencing, thus making them less comfortable and relaxed. It

is also unusual that subjects reported feeling more alert and calm following smoking a cigarette as previous studies report subjects feeling increased calmness or alertness, but not increases in both mood dimensions. A range of subjective mood experiences have been reported to accompany acute and chronic smoking withdrawal states and subjects may have felt drowsy and irritated during the acute deprivation period. Under these acute smoking deprived conditions, smoking a single cigarette may well increase alertness and may also reduce these uncomfortable feelings, allowing them to function more efficiently and help them to better deal with the day.

Craving self-ratings produced similar results to previous studies in that craving was reduced overall, following smoking a real cigarette as compared to sham smoking (Dawe, Gerada, Russell and Gray, 1995). That this occurred in both placebo and haloperidol conditions suggests that the dopaminergic system may not be involved in the processes regulating cigarette cravings, either for withdrawal reductions or mood regulatory purposes. Euphoria self-ratings revealed higher euphoric feelings following smoking than following sham. However, this was not a result of increased euphoric feeling following real smoking, but rather a decrease in euphoria following sham smoking. MBG-assessed euphoric responses have been shown to be marked with opiates, marijuana and stimulants, only moderately evidenced with alcohol, barbiturates and hallucinogenics, and have been relatively absent with tranquilizers (Haertzen and Hickey, 1987). Given that the euphoric response was not evident with acute smoking, even in the deprived smoking state, it can be reasonably

argued that euphoria is neither a necessary or sufficient affective state for the initiation or maintenance of the smoking habit.

Appraisal of the sensory/liking aspects of cigarette smoking was similar in both placebo and haloperidol conditions. Inhaled cigarette smoke, because of its distinctive taste, aroma and irritant 'scratch' properties in the throat, is a key sensory cue which has been shown to be critical in providing immediate satisfaction of smoker's craving for cigarettes (Nemeth-Coslett, et al., 1986). Given the negative effect of haloperidol, and as previous reports have shown that mecamylamine reduced ratings of nicotine gum strength (Pickworth, et al., 1988) and cigarette satisfaction (Nemeth-Coslett, et al., 1986) while combined mecamylamine/scopolamine administration reduced ratings of cigarette strength (Knott, et al., 1998b), it appears that cholinergic, not dopaminergic systems, play a more important role in the regulation of sensory reward properties associated with the smoking habit.

The correlation between EEG measures and self-ratings of mood were, in general, comparable to that reported in previous research (Knott, et al., 1998b). Of particular interest with respect to the support of a functional versus an addictive model of cigarette smoking was the observation that smoking-induced α_2 amplitude increments were positively correlated with smoking-induced subjective alertness ratings but were negatively related to euphoric ratings. Although the function of significance of each spectrum is unknown, smoking and nicotine have been consistently found to improve behavioural performance on a range of cognitive tests, including tasks of short and long term memory

(Pritchard and Robinson, 1998). This complies with the available evidence on α_2 which has shown increased activity in the band to be sensitive to processes related to searching, accessing and retrieving information from memory (Klimesh, 1997). The correlation between euphoria ratings following smoking and smoking-induced EEG changes is, however, somewhat inconsistent, with the main ANOVA results reported with the euphoria scale alone. Upon observation of the scatterplot of euphoria and post-smoking EEG changes, as seen in Figure 7, the data seems to be concentrated in two pockets, and the euphoria scale does not appear to be producing particularly robust results. Therefore, this correlation may not be particularly accurate.

Insert Figure 7 about here

The only smoking-induced EEG component blocked with haloperidol pretreatment was absolute beta amplitude. This appears to provide support for a previous report of the involvement of dopamine in the physiological effects of nicotine (Ferber and Kuschinsky, 1997). Although the blocking of beta incrementation, an electrocortical response typically seen in high arousal/task activation conditions, may well be related to inhibition of dopamine release, the interaction of transmitter systems makes this interpretation somewhat less than definitive. An obvious interaction exists between the release of dopamine and acetylcholine (from both muscarinic and nicotinic receptors) in the midbrain, specifically the striatum (Ikarashi, Takahashi, Ishimani, Arai and Maruyana,

Figure 7. Smoking-induced euphoria (MBG) ratings and smoking-induced absolute EEG (alpha₂) amplitude changes.

1997; Picciotto, et al., 1998), ventral tegmental area (Gronier and Rasmussen, 1998; Pidoplinchko, DeBiasi, Williams and Dani, 1997) and nucleus accumbens (Corrigall, Franklin, Coen and Clarke, 1992). Following ingestion of nicotine, it has been shown in these animal studies that nicotine produced the release of acetylcholine which results in the release of dopamine from the mesolimbic dopamine system, a system thought to be responsible for the reward mechanisms associated with various addictive drugs, including amphetamine, morphine, cocaine and nicotine (Gardner, 1997). While nicotine stimulates dopamine release in the ventral striatum in normal animals, mice lacking the $\beta 2$ -subunit of the high-affinity neuronal nicotinic receptor, a subunit thought to be responsible for the release of dopamine following ingestion of nicotine, no longer had the dopamine release response associated with nicotine (Picciotto, et al., 1998). Another study found that antagonism of D_2 dopamine receptors increased the acetylcholine release in a dose dependent manner, while a dopamine D_2 receptor agonist inhibited acetylcholine release, also within the striatum (Ikarashi, et al., 1997). Investigating the effect of a dopamine antagonist alone and in combination with an acetylcholine agonist and/or antagonist may help to further delineate the specific role of dopamine in smoking-related reward. As it has been reported that the effect of Haldol on drug-free schizophrenics has a different effect for acute dosing as compared to long-term use (Galderisi, Mucci, Mignone, Maj and Kemali, 1992), it may also be interesting to see the long-term effect of a dopamine antagonist on the smoking-induced neuroelectric response in normal individuals. A relatively recent study

suggests that the EEG blocking ability seen with acute Haldol may exhibit tolerance, as the smoking-induced EEG activation profile was fully apparent in schizophrenia patients chronically treated with dopamine antagonists (Knott and Harr, 1995).

Of course other neurotransmitter systems may act separately or in combination with dopamine or acetylcholine to produce the smoking-induced EEG activation response and the myriad of subjective/behavioural responses which accompany smoke inhalation. As shown in the figure schematic (see figure 8) the available evidence to date suggests that each EEG spectrum component altered by acute smoking/nicotine appears to be sensitive to different neurotransmitter systems, with the slow frequency response component being mediated by acetylcholine, while a high frequency response being mediated by dopamine. The alpha band activities have more or less exhibited resilience to

Insert Figure 8 about here

the blockade of each of these transmitter systems, suggestive perhaps that their respective reemergence may be controlled by other transmitters acting separately or in combination with acetylcholine and/or dopamine. In this respect, it is of interest to note that bupropion (Zyban), an antidepressant with noradrenergic and dopaminergic augmenting properties has been found efficacious as a smoking cessation agent (Raymond, et al., 1999) and, in separate studies has been found to increase global alpha amplitude (Saletu, 1987). Investigating

Figure 8. The putative effects of different neurotransmitters on the smoking-induced EEG (absolute amplitude) activation profile following placebo pretreatment. Acetylcholine (Ach) appears to modulate the slow wave activity (delta, theta) component, while dopamine (DA) seems to modulate the fast wave activity (beta) component. Noradrenaline (NA) may have an effect on alpha₂ rhythm.

central noradrenergic blockers alone or in combination with dopamine and cholinergic antagonists may be a promising route to examining the role of this system in the regulation of brain and behavioural processes underlying the smoking habit.

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Appendix A

INFORMED CONSENT FOR EXPERIMENTAL SUBJECTS

Title of Study: Effects of Acute Haloperidol Administration on the Smoking-Induced EEG/Mood Activation Response Profile

Principal Investigator: D. R. Walker, BSc (Spec.)

Co-Investigators: Dr. V. Knott - Advisor
Dr. D. McIntyre - Co-Advisor
Dr. Illivitsky, Medical Doctor, ROH

Description of Study: The physiological and psychological effects produced by nicotine have been well documented, but the reasons as to why these effects occur are still somewhat of a mystery. Following administration of nicotine, many chemicals which may cause the effects associated with smoking are released into the brain. By selectively blocking the release of one of these chemicals, it may be possible to examine the effect that this chemical has on the smoker. Dopamine is one such chemical which is increased by smoking and it is believed that such increases may account for the pleasurable effects of smoking.

Haloperidol is a psychotropic drug which is used to treat a variety of mental disorders which are believed to be caused by too much dopamine. Administration of haloperidol reduces dopamine's effect on the brain and behaviour. The purpose of the current study is to see if a single dose of haloperidol changes the brain activation and mood altering effects of cigarette smoking. It is believed that this research will provide us with more information on the brain chemistry responsible for smoking addictions.

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 which will be one week apart. You will be asked to abstain from smoking, caffeine, alcohol, drugs and medication (for example, Aspirin or herbal medication) 12 hours before each morning test session. In the two test sessions which begin at 8:00am, sensors will be placed on your scalp and around your eyes. You cannot feel the electrodes working and you cannot get a shock from them. Once the sensors are in place, the first of three assessments will be carried out. You will then be asked to sit and relax with eyes closed for a brief period and rate your mood on a questionnaire.

During each of the two test sessions, you will be given either a placebo mixed with orange juice (containing no active substance) or you will be given haloperidol mixed with orange juice (the active substance, which is capable of reducing the effects of dopamine on brain activity). You will be administered the placebo or haloperidol in a random order and neither you nor the doctor or research staff will know when you are receiving haloperidol or placebo. Once you have swallowed the drug, you will wait for 120 minutes (watching

videos or reading) until the substances are absorbed into your blood. After 120 minutes, you will be asked to 'sham' smoke (inhale on a non-lighted cigarette) for 5 minutes and then a second assessment will be carried out. After the second assessment you will be required to smoke one of your own cigarettes and then a final assessment will be conducted. The third assessment will also include questions about the cigarette smoking itself, e.g., Was it harsh on your throat? Each session will last approximately 4 hours.

Possible Risks Involved: The risks are minimal. The main side effects which may be experienced with a single dose of haloperidol are sleepiness/sedation, low blood pressure, dry mouth, blurred vision, constipation, difficulty urinating, stiffness, anxiety/agitation, difficulty moving. More rare side effects include dizziness, racing heart/palpitations, weakness, sexual problems, restlessness, skin rash, tremors and involuntary facial/tongue movements. These side effects which some subjects may experience are temporary (usually not lasting more than 24 hours maximum). It is unlikely subjects in this study will experience all of them with a single dose and it is quite possible that none of them will be experienced. If acute dystonia is experienced from the haloperidol, Dr. Ilivitsky will administer a medication to counteract these adverse effects.

The EEG monitoring is very similar to what is carried out in general hospitals except that it is analysed by computer. The sensors placed on your scalp and skin may cause a mild and temporary irritation and redness of the skin which will disappear in a few hours.

You will be asked to refrain from caffeine and smoking from midnight preceding each test session. Such abstinence may increase your craving for cigarettes and you may feel slightly irritable, drowsy and distracted. Because haloperidol may cause you to feel drowsy, we ask you to refrain from any activities which require mental alertness such as operating any machinery or driving for a minimum of 24 hours following administration of the drug.

Participation: Your participation is voluntary and you will be free to withdraw from the study at any time.

Confidentiality: Information will be coded and your privacy will be protected. Any scientific publications from this work will be so designed that your anonymity will be preserved.

If you have any concerns or questions about this study, you should contact the principal investigator, Darlene Walker (722-6521 ext.6928), or the advisor, Dr. Knott (722-6521 ext 6843). If you have any ethical concerns, you can contact the Chair of the Ethics Committee, Carleton University, Dr. M. Gick (520-2600, ext. 2664), or the Chair of the Psychology Department, Dr. K. Matheson (520-2600, ext. 2648).

CONSENT FORM

**Study Name: Effects of Acute Haloperidol Administration on the
Smoking-Induced EEG/Mood Activation Response Profile**

Statement: I, _____, agree to participate in the above described research project, the nature and possible complications of which have been explained to me.

I also consent that any data collected as a result of my participation in this project may be utilized for education and/or scientific purposes.

I have received assurance that my anonymity will be preserved in the use of this material.

I also understand that the possible effects of the medication are temporary. Therefore I agree to abstain from any activities that require mental alertness such as driving a motor vehicle or operating dangerous machinery until the day after each test session. I also understand that alcohol and drugs may intensify side effects (e.g., Aspirin or antacids containing aluminium or magnesium) and I agree to abstain from alcohol and drugs until the day after each test session. I also understand that a physician will be part of the study and involved in treating any adverse reaction that should occur. This may involve the administration of Cogentin if acute dystonia is experienced with haloperidol.

I have received assurance that I may withdraw from participation at any time.

Date

Signature of Research Participant

Date

Signature of Principal Investigator

Date

Signature of Witness

Appendix B

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing the full range of each dimension.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.

Alert	_____	Drowsy
Calm	_____	Excited
Strong	_____	Feeble
Muzzy	_____	Clear-headed
Well-coordinated	_____	Clumsy
Lethargic	_____	Energetic
Contented	_____	Discontented
Troubled	_____	Tranquil
Mentally Slow	_____	Quick-witted
Tense	_____	Relaxed
Attentive	_____	Dreamy
Incompetent	_____	Proficient
Happy	_____	Sad
Antagonistic	_____	Amicable
Interested	_____	Bored
Withdrawn	_____	Gregarious

Appendix C

This inventory consists of numbered questions. Read each question carefully and decide whether it is TRUE as applied to you right now or FALSE as applied to you right now.

If the statement is TRUE or MOSTLY TRUE as applied to you, circle T for TRUE.

If the statement is FALSE or MOSTLY FALSE as applied to you, circle F for FALSE.

Remember to give YOUR OWN OPINION of yourself. DO NOT leave any blank spaces.

Correct marking of answers.

A	T	F
B	T	F

Remember, answer every question according to the way you feel right now. Be as accurate as possible.

1. I would be happy all the time if I felt as I feel now.	T F
2. I am in the mood to talk about the feeling I have.	T F
3. I am full of energy.	T F
4. I would be happy all the time if I felt as I do now.	T F
5. Things around me seem more pleasing than usual.	T F
6. I feel less discouraged than usual.	T F
7. I fear that I will lose the contentment that I have now.	T F
8. I feel as if something pleasant had just happened to me.	T F
9. Today I say things in the easiest possible way.	T F
10. I feel so good that I know other people can tell it.	T F
11. I feel more clear-headed than dreamy.	T F
12. I can completely appreciate what others are saying when
I am in this mood.	T F
13. I feel as if I would be more popular with people today.	T F
14. I feel a very pleasant emptiness.	T F

15. I feel in complete harmony with the world and those around me.

T F

16. I have a pleasant feeling in my stomach.

T F

17. I feel high.

T F

Appendix D

Cigarette Craving Questionnaire

Subject No.

Questionnaire No.

Date/...../1998

Please answer these questions by placing a vertical mark on the appropriate line as indicated in the following example.

- 1. How much have you been craving a cigarette?**

- 2. How much have you been craving a cigarette because you feel anxious?**

- 3. How much have you been craving a cigarette because you feel drowsy?**

- 4. How much have you been craving a cigarette because you feel irritable?**

- 5. How much have you been craving a cigarette because you feel sad?**

- 6. How much have you been craving a cigarette because you feel unfocused?**

Appendix E

Cigarette Appraisal Questionnaire

Subject No. Questionnaire No. Date / / 1998

Given below are a number of questions which relate to different aspects of the cigarettes you are currently smoking. Please answer these questions by placing a vertical mark on the appropriate line as indicated in the following example.

is would indicate
Neither property
This would indicate
a strong property

1. Effect on throat

Too little
Too much
2. Strength

Too mild
Too strong
3. Flavour

Dislike
Like
4. Smoothness

Too smooth
Too rough
5. Hotness

Too hot
Too cool
6. Ease to draw

Too easy
Too hard
7. Liking

Dislike
Like

Do you think that the taste or flavour of the cigarette changed while you smoked it?

Yes..... **No.....**

If 'Yes', was this change: Slight..... Moderate..... Very Marked.....