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Internal tobacco industry research on olfactory and trigeminal nerve response to nicotine and other smoke components

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Abstract

Evidence has shown that factors other than the central pharmacological effects of nicotine are important in promoting smoking behavior. One such non-nicotine effect includes sensory stimulation, which may promote smoking by developing learned associations with nicotine's rewarding effects, or by constituting a rewarding experience independent of nicotine. The present study used internal tobacco industry documents to examine industry efforts to understand and manipulate stimulation of the sensory nerves by tobacco smoke, and the influence of sensory stimulation on smoker behavior. Research focused on sensory nerves of the head and neck, including the olfactory nerve, which carries flavor and odor, and the trigeminal nerve, which carries irritant information. The tobacco industry maintained a systematic research program designed to elucidate an understanding of responses of sensory nerves to nicotine and other components of tobacco smoke, and attempted to develop nicotine-like compounds that would enhance sensory responses in smokers. Industry research appeared intended to aid in the development of new products with greater consumer appeal. The potential influence of sensory response in enhancing nicotine dependence through an associative mechanism was acknowledged by the tobacco industry, but evidence for research in this area was limited. These findings add to evidence of industry manipulation of sensory factors to enhance smoking behavior and may have implications for development of more effective treatment strategies, including more "acceptable" nicotine replacement therapies.

Introduction

Considering the relative recency with which tobacco use has come to be understood as addictive (American Psychiatric Association, 1994; U.S. Department of Health and Human Services, 1988), much progress has been made in elucidating the neurobiological

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basis for nicotine dependence. Evidence compiled since the early 1980s has shown that nicotine exerts powerful positive reinforcing effects in animals (e.g., Goldberg, Spealman, & Goldberg, 1981) and humans (e.g., Harvey et al., 2004), and that such effects are mediated largely via activity at nicotinic acetylcholine receptors located within the mesolimbic dopamine pathway (e.g., Corrigall, 1991). Nicotine administration increases dopamine in the shell of the nucleus accumbens (Balfour, 2004), which is associated with a hedonic response common to major drugs of dependence (Nestler, 2005). Such acute, positively rewarding effects are important in promoting self-administration behavior, and they provide a widely accepted mechanism for nicotine dependence (Balfour, 2004).

Nevertheless, evidence suggests that factors other than central pharmacological influences of nicotine are important in promoting smoking behavior. One key line of evidence underpinning this idea is the observation that nicotine replacement therapy has only a weak effect in overcoming tobacco dependence (e.g., Bohadana, Nilsson, Rasmussen, & Martinet, 2000; Croghan et al., 2003). Rose and colleagues (e.g., Rose, 2006) have argued that reinforcement independent of the primary effects of nicotine is available through smoking. So-called non-nicotine effects could include sensory stimulation as well as other pharmacologically active components of cigarette smoke. For example, smokers may regulate their smoking behavior according to sensory intensity rather than nicotine intake (Rose, Behm, Westman, Bates, & Salley, 2003).

In support of this hypothesis is research showing that smokers perceive the sensory effects of denicotinized cigarettes similarly to those of conventional cigarettes, despite the lack of a pharmacological influence from nicotine (Rose, Behm, Westman, & Johnson, 2000). Denicotinized cigarettes may reduce tobacco craving and withdrawal through exposure to subjective elements of exposure to tobacco smoke (Westman, Behm, & Rose, 1996). Indeed, sensory factors may be even more important among highly dependent smokers, given that ratings of smoking satisfaction of denicotinized cigarettes vary positively with level of tobacco dependence (Rose, Behm, & Levin, 1993). Such findings highlight the importance of sensory cues in the determination of smoking satisfaction (Rose & Behm, 2004), psychological reward (Brauer et al., 2001), and craving reduction (Levin et al., 1993). Sensory and subjective effects of tobacco products appear to play an important role in enhancing smoking behavior independently of the central effects of nicotine, and suggest that activity at sensory nerve sites may provide an important contribution to smoking behavior.

Sensory cues can arise from a range of neural responses including smell (via olfactory nerve), irritation (trigeminal nerve), and taste (facial, glossopharyngeal, and vagal nerves). Although sometimes associated with pleasure and satisfaction, stimulation of sensory nerve networks is not usually regarded as sufficient to support behavior regarded as addictive. However, sensory cues may develop incentive value through a learned association with centrally mediated drug reward. Associative learning mechanisms provide an important means by which addiction to tobacco might be understood (West, 2006). Sensory stimuli that are paired repeatedly with nicotine’s central effects (unconditioned stimuli) can themselves come to acquire motivational significance and promote smoking-related behavior. For example, craving and drug-appetitive behaviors are known to be elicited by

exposure to drug-associated cues (conditioned stimuli; e.g., Drummond, 2001; Stewart, de Wit, & Eikelboom, 1984). Robinson & Berridge's (2001, 2003) incentive-sensitization theory suggests that sensory stimuli can acquire "incentive salience," allowing sensory cues to represent a profound psychological reward state termed drug wanting. Because of their association with drug reward, sensory cues may come to promote drug-using behavior and, potentially, enhance the unconditioned rewarding effects of nicotine. A recent alternative theory has suggested that nicotine may enhance the capacity for unconditioned cues such as sensory stimuli to promote drug-use behavior, even without learning of specific nicotine-cue associations (Chaudhri et al., 2006).

The success of the tobacco industry in exploiting strategies to enhance smoking through products that are more addictive or carry greater consumer appeal is well recognized. Internal tobacco industry documents made publicly available through litigation have provided the larger scientific community with a unique opportunity to assess the underlying objectives and strategies of the tobacco industry and opened new pathways for research. Research of internal documents has shown that manufacturers have manipulated cigarette design—including factors such as appearance, flavor, and smoke characteristics—to enhance consumer acceptance. Tobacco manufacturers have significantly enhanced the addictive potential of their products through increased nicotine delivery (Keithly, Ferris Wayne, Cullen, & Connolly, 2005), greater ease of inhalation (Ferris Wayne & Connolly, 2004), and increased bioavailability of nicotine as well as other potential reinforcing agents (Keithly et al., 2005).

Internal tobacco industry research has likewise demonstrated behavioral strategies by which nicotine dependence can be enhanced. Cook, Ferris Wayne, Keithly, & Connolly (2003) described the tobacco industry's identification and subsequent use of varying psychological and psychosocial needs of consumers to better target products to individuals. Ferris Wayne, Connolly, & Henningfield (2004) documented industry knowledge of the psychological, behavioral, and pharmacological mechanisms of tobacco dependence, including industry investigations into central nervous and peripheral actions of nicotine, and the role of nicotinic receptor activity on behavioral outcomes. These and other findings demonstrate the industry's comprehensive understanding of nicotine pharmacology, smoker psychology, and psychosocial aspects of tobacco use.

This study describes internal tobacco industry research efforts to understand and manipulate stimulation of the sensory nerves by tobacco smoke, and its potential influence on smoker behavior. Research targeted major nerves of the head and neck, with the olfactory and trigeminal nerves considered the principal candidates for stimulation. Although nicotine itself possesses both odorant and irritant qualities, the study also sought to identify internal research on non-nicotine smoke constituents that had direct actions on sensory nerve systems, including the capacity to mimic the sensory effects of nicotine. Evidence for industry attempts to identify alternative potential mechanisms for sensory nerve involvement in smoker behavior, such as research on associative learning phenomena, also was explored. Given mounting evidence supporting the importance of sensory stimulation on smoker behavior, we hypothesized that internal studies of sensory activity would have relevance for product development, particularly in relation to the development of "low yield" or reduced

harm products, as well as industry targeting of sensory needs identified within specific smoker populations.

Method

A snowball sampling method, in which a set of relevant documents was identified by expanding initial searches of general key words and related synonyms (Table 1), was used to conduct Web-based, full text searches of more than 7,000,000 internal tobacco documents made publicly available through state litigation and the 1998 Master Settlement Agreement (MSA) between the states' attorneys general and the major U.S. tobacco manufacturers. According to the MSA, newly released documents from civil litigation are continuously added to archival databases such as that maintained by Tobacco Documents Online (www.tobaccodocuments.org), the primary Web site used in this study.

Documents were chosen based on their relevance in three major categories: (a) nicotine and non-nicotine smoke constituents demonstrating actions on sensory nerve systems in the face and neck (i.e., olfactory, trigeminal, vagal, glossopharyngeal, and facial nerves); (b) the role of sensory nerve stimulation in influencing responses to nicotine and smoking behavior, via multiple potential mechanisms; and (c) the relationship of research on sensory nerve stimulation to product development. Recurring authors, projects, and research proposals were identified when possible to discover further avenues for study. The study resulted in a final set of approximately 150 documents spanning from 1972 to 1997, gathered from the major U.S. tobacco manufacturers (Philip Morris, R. J. Reynolds Tobacco Company, Brown & Williamson, and Lorillard).

As with any document-based study, our conclusions are limited only to documents available to the public, which may represent an incomplete picture of internal research and findings. In particular, the absence of research available after 1997 may suggest a potential lack of accessibility to recent documents, rather than the absence of industry research during this period. Care also must be taken in drawing conclusions based on internal studies that represent disparate authors, companies, and time periods.

Results

The tobacco industry developed a sophisticated understanding of sensory responses to tobacco smoke and their neurophysiological bases. A primary internal objective was to relate subjective response to product characteristics, or as described in a 1990 Philip Morris presentation: "We need to know what is important in smoke in order to delve into what is important flavor-wise in tobacco" (Philip Morris, 1990). For example, a 1987 R. J. Reynolds document claimed that the trigeminal response combined with those of taste and olfaction to produce the subjective concept known as flavor (R. J. Reynolds, 1987). A Philip Morris scientist further described the manufacturer's interest in characterizing trigeminal nerve responses, noting that these findings could be used to predict actions on the glossopharyngeal nerve and the vagus nerve (Gullotta, 1990b). Table 2 describes manufacturer efforts to determine the sensory impact of nicotine and other smoke constituents, particularly on the olfactory and trigeminal nerves.

Sensitivities of the olfactory and trigeminal systems to tobacco, nicotine, and other chemicals

Early industry research was aimed at identifying sensitivities of the olfactory and trigeminal systems to nicotine and tobacco smoke. By conducting experiments in which an odor was placed in one nostril and an irritant in the other (dichorhinic stimulation), researchers at R. J. Reynolds found that, at very low levels, the senses were additive but that irritation inhibited the perception of odor as concentration levels increased, “indicating that this interaction does not occur at the receptor level but more centrally in the nervous system” (R. J. Reynolds, 1987). Other industry-supported studies showed low concentrations of nicotine evoking an olfactory response, whereas higher concentrations induced burning and stinging sensations (Hummel, Hummel, Pauli, & Kobal, 1992). Furthermore, in experiments in which the olfactory nerves were transected, odorant response—now mediated primarily by the trigeminal system—showed decreased sensitivity, thereby indicating the greater sensitivity of the olfactory system (Walker, Walker, Tambiah, & Gilmore, 1986).

Several research teams subsequently proposed using an olfactometer to compare odorant sensitivities of normal, anosmic (olfactory nerve removed), and anosmic-trigeminectomized (both olfactory and trigeminal nerves removed) pigeons, and to compare odorant discrimination abilities of normal and anosmic pigeons. They suspected that the olfactory and trigeminal nerves are differentially affected by stimulation, and that nasal trigeminal chemoreceptors are entirely responsible for odorant detection in anosmics of both pigeon and human models (R. J. Reynolds, 1990). As summarized by an R. J. Reynolds scientist: “Subjects lacking a sense of smell (anosmics) have much greater detection thresholds for most odorants. Anosmics report thresholds at ‘irritating’ concentrations since only the trigeminal nerve receptors are reporting to the brain” (Jennings, Morgan, & Walker, 1991).

Published experiments have demonstrated that both R(+) and S(−) nicotine stereoisomers can be distinguished by the test subject even though detection thresholds of these stereoisomers are quite similar (Hummel et al., 1992). In response to a scarcity of research examining the effects of nicotine on the olfactory and trigeminal systems, research supported by Philip Morris sought to clarify whether the olfactory system was responsible for the mammalian ability to differentiate among nicotine stereoisomers (Kobal, Renner, & Thurauf, 2004). After recording electroolfactogram (EOG) oscillations in frogs induced by odorant stimulation (distilled S(−)-nicotine, undistilled S(−)-, distilled R(−)-nicotine) at different concentrations, responses to undistilled S(−)-nicotine were reported as significantly lower than responses to the two distilled nicotine isomers, and no EOG differences were evident among the purified stereoisomers. Because similar results were found in humans by the same researchers in an identical experimental setup, the authors claimed that the differentiation of the stereoisomers of nicotine must be mediated by the trigeminal system (Kobal et al., 2004). Three years later, researchers also funded by Philip Morris found that the differentiating role of the olfactory system cannot be completely ruled out, as small differences, although not detected by the EOG, may be sufficient for the discrimination of the nicotine stereoisomer (Barocka, Dietz, Kaegler, Kobal, & Thurauf, 1997).

Scientists at Philip Morris noted that the olfactory nerve is unique in that it sends information ipsilaterally. Whereas all other nerves, including the trigeminal, pass

contralaterally, an olfactory stimulus presented to the left nostril, for example, would project a nerve impulse to the left hemisphere of the brain. This differentiation might determine which system was primarily activated given a stimulus. Researchers analyzed nasal event-related potentials (NERPs)—often used to obtain information about flavor discrimination—of four different compounds at five concentrations each. The compounds included phenyl ethyl alcohol, dimethyl anthranilate, isoamyl acetate, and CO_2. All responses were amplified as concentrations increased, and all but CO_2 were found to produce primarily an olfactory response. The authors claimed the importance of these responses in determining "which potential flavorants have feeling factors in an entirely objective manner…and in which concentrations they do so." They concluded: "This capability might be very important in looking for things like nicotine replacements, and also in designing flavor systems for some of our new products" (Gullotta, 1990b). Of the compounds tested, ethyl alcohol and isoamyl acetate are noted on a list of additives by Philip Morris used in the manufacture of tobacco products and their substitutes (Farnham, 1995).

Armed with the ability to differentiate olfactory from trigeminal sensory activation, scientists then sought to clarify mechanisms of physiological responsivity by the study of puff profiles. Puff profiles are used to determine how a cigarette is smoked by the subject and are frequently analyzed to improve product design and acceptability. Researchers at R. J. Reynolds concluded that the most important activity during a puff occurred at the oral trigeminal chemoreceptors (Walker, 1990). A pilot study conducted in 1991 measured puffing behaviors in the presence of an oral stimulant and under conditions of slightly lower pressure. Puffing resistance was determined in five subjects when water or ethyl alcohol aerosols were generated by a nebulizer and puffed through glass depressurized tubes. Results verified prior reports by showing that "in a simplified model cigarette, one of the sensory cues that determines perceived resistance to a puff is the chemosensory stimulation of the oral cavity" (Jennings et al., 1991).

Trigeminal and olfactory screening of nicotine analogs and new compounds

Further research on the trigeminal and olfactory nerve systems was intended to identify new compounds that shared or improved upon nicotine's sensory stimulant qualities. Tobacco manufacturers used animal models to measure sensory responses to nicotine and its analogs, in an effort to find a possible sensory substitute for nicotine. One of Philip Morris's main research objectives in the early 1990s was to "distinguish between nicotine as a chemosensory stimulant and nicotine as a nicotinic cholinergic agonist" (Philip Morris, 1995a). More specifically, scientists sought to determine whether bitter taste sensation was caused by nicotine—or other bitter-tasting compounds—binding to nicotinic cholinergic receptors (nAChRs) on trigeminal nerve endings on taste cells, or by interactions with noncholinergic receptors in the apical regions of taste cells (Philip Morris, 1995c). The first possibility was hypothesized to be the case, although final conclusions from the proposed experimental study were not identified in the internal documents.

Philip Morris–funded studies also sought to characterize the bitter-tasting properties of nicotine to compare them to similar compounds and possibly better elucidate the correct biochemical pathway of bitter-tasting compounds (Abood, 1995). Several proposals to

look further into the sensory effects of nicotine on the tongue, pharmacology of nicotine irritation, and interaction with nicotine and menthol in humans and rats resulted (Carstens & Omahony, 1996). Although final experimental results were not identified in the current review for some proposals (Philip Morris, 1996), others funded by Philip Morris led to the successful testing of irritant compounds relative to nicotine (Carstens, Dessirier, & Omahony, 1996).

In studies funded by R. J. Reynolds in the late 1980s, Silver and colleagues (Silver, 1988; Silver, Walker, Ogden, & Walker, 1988) examined the respiratory and electrophysiological responses of rats to nicotine, amyl acetate, and toluene in an effort to understand trigeminal chemoreception in the nasal cavity. In contrast to amyl acetate and toluene, nicotine elicited a ceiling response, from the ethmoid branch of the trigeminal nerve, even at lower test doses. Nicotine exposure also resulted in a longer baseline recovery period in the ethmoid nerve, which is primarily responsible for sensory innervation to the internal nose. Accordingly, the scientists concluded, “Nicotine is the most effective trigeminal stimulus, and perhaps the most irritating” (Silver, 1988). Silver and colleagues also reported that, although neural responses were seen at low concentrations, respiration changes did not occur at the lowest concentrations for all three test compounds, suggesting that the trigeminal nerve can be stimulated without affecting breathing (Silver et al., 1988).

At about the same time, Philip Morris began a process called trigeminal screening as part of Project ART in 1989 to more rapidly screen compounds that could be detected by smell. A ballot with a list of trigeminal descriptors had been prepared for the project, and analysis for all promising compounds was planned using a vapor-dilution olfactometer (Gullotta, 1989). A preliminary report on the trigeminal screen indicated that 25 compounds had already been tested for trigeminal nerve or olfactory stimulation, and that researchers were able to differentiate trigeminal and olfactory stimulation. This allowed a more finely tuned means for distinguishing different classes of compounds (Gullotta, Jeltema, & Southwick, 1989). Philip Morris scientists confirmed the importance of the trigeminal screen with the discovery of 4 compounds (out of 30 tested) that “mapped near nicotine in the trigeminal multidimensional space” (Southwick, 1991). However, researchers expressed their surprise that of the four compounds (n-butylidenephthalide, pyridine, phenylacetic acid, and 1-[3-methylbutyryl] pyrrolidine), none had the same functional group and, with the exception of pyridine, all differed from nicotine. Thus, although they were “perceived to be as ‘prickly’ as nicotine; none exhibited [its] full sensory properties” when tested in cigarettes (Southwick, 1991).

In an earlier study, gas chromatography was used to separate cigarette smoke into over 600 components, which were then evaluated for their olfactory characteristics. The concentration of smoke in a majority of the components was reported below the threshold for olfactory perception (Farnham, Apmo, Artho, Koch, & Kox, 1983). R. J. Reynolds had a similar agenda for finding the most effective odorants. Scientists in 1984 found the response thresholds of eight n-aliphatic alcohols to decrease with increasing carbon chain length (6,000 ppm for methanol, 35 ppm for octanol) whereas response magnitudes increased for individual compounds and latencies decreased with increasing stimulus concentrations. Noting that “increasing lipophilicity results in increasing stimulus effectiveness,” they

hypothesized that penetration of the mucous and epithelial layers allowed more effective access to chemosensitive trigeminal nerve endings (R. J. Reynolds, 1984). These findings strengthened the already persistent argument among tobacco scientists that nicotine's stimulatory effects on the various senses were attributable to its lipophilic character (Heckman, Best, Schumacher, & Piehl, 1978).

In the 1990s, Philip Morris scientists investigated nicotine and other bitter tastants, such as capsaicin (hot pepper), to determine if a trigeminal sensation such as irritation resulted from nicotine binding to receptors in pain fibers called nociceptors (Philip Morris, 1995b). Another 1995 study funded by Philip Morris, in which scientists performed whole-cell patch clamp recordings on rat trigeminal ganglion cells, determined that "about 20% of the total number of neurons tested were activated by both 100 mM nicotine and 1 mM capsaicin." As other subunits of neurons were activated by only one or neither compound, the researchers confirmed the existence of subunits of capsaicin-sensitive afferent neurons (Liu, & Simon, 1995).

Earlier industry research had shown differing sensory impacts on nicotine-deprived and nondeprived individuals, depending on the concentration of nicotine administered (Gullotta, 1982). Accordingly, in 1996, scientists funded by Philip Morris conducted an experiment to evaluate the changes in irritant sensations by repeated applications of nicotine and capsaicin on the human tongue. Research showed that capsaicin treatment caused sensitization, or a greater response after repeated application, whereas nicotine caused adaptation, or a significantly smaller response after repeated application. Moreover, nicotine was found to cause weaker sensation in the trigeminal nerves after pretreatment with capsaicin, whereas capsaicin continued to cause greater sensations following nicotine pretreatment (Carstens et al., 1996). This finding corresponded to those from earlier R. J. Reynolds experiments with chemical irritants, which showed a "greater degree of specificity of trigeminal receptors than was previously thought." For example, in experiments with capsaicin and piperine, scientists reported a significant increase in subjective irritation when a second irritant was presented that differed from the first, as compared with controls in which the irritant did not change (Kurtz, Walker, & Ogden, 1987). We found no indications that capsaicin or piperine studies resulted in the use of either compound as an additive.

Application of sensory nerve research to addiction enhancement and product design

Although cigarette smoking was understood internally as, essentially, nicotine-seeking behavior (Ferris Wayne et al., 2004), programs beginning in the mid-1970s sought to identify the full range of factors contributing to reinforcement, including "taste and olfactory elicitations, psychosocial symbolism" as well as "a large number of chemical compounds passing through the lungs" (Philip Morris, 1997). This internal research reflected the manufacturers' increasingly comprehensive outlook on the role of sensory nerve stimulation in the development and persistence of a smoker's behavioral response. An important target of sensory research was the contribution of peripheral nerve responsivity to the total behavioral phenomenon (Philip Morris, 1995a; R. J. Reynolds, 1987). For example, a 1995 Philip Morris document described a series of research proposals to identify the sensory characteristics of nicotine and their contribution (alongside other stimuli) to smoker

responses. One proposed study sought to relate exposure to “the flavor components of their preferred brands” (Philip Morris, 1995a) to a Pavlovian-type salivary response.

Industry knowledge of associative learning factors in smoking behavior included the use of nicotine as a reinforcer for conditioning of taste aversions (Stuhl, 1984). Scientists at R. J. Reynolds speculated on the role of conditioned taste aversions (CTA) in promoting smoking behavior:

> [C]oncerning the role of the CTA methodology to the “real life smoking situation”, it is not farfetched to say that the habitual smoker usually identifies a distinct taste with a certain cigarette brand and/or cigarette type (e.g. “Virginia-type”) and therefore, when switching from one brand to another, situations like the one described as conditioned taste aversion, conceivably, happen to him. (Stuhl, 1984)

A 1987 R. J. Reynolds report on taste and olfaction described the modulation of the olfactory bulb from multiple brain areas (the olfactory cortical areas, the basal forebrain and the midbrain), such that an odor may have a different meaning depending on the existing state of behavior. The authors observed: “Much of a person’s emotional/psychological reaction to odors, other than noxious or irritating odors, is learned. A person’s reaction to an odor will depend on past experience, as well as current environment, physical and mental state.” Furthermore, the authors reported that the olfactory system of the rat has been shown to play an important role in a number of emotional behaviors, and this “appears to be independent of sensory processing. Removal of olfactory bulbs from rats causes the animals to be more difficult to handle. This effect does not seem related to the loss of odor perception since rats subjected to peripheral anosmia (loss of sense of smell) fail to show these changes” (R. J. Reynolds, 1987).

Growing understanding of sensory mechanisms and their contribution to reinforcement was then applied by manufacturers to the development of more effective products. Thus, before 1990, R. J. Reynolds outlined, as part of its future operating plan, a program to undertake basic sensory research, and “develop fundamental knowledge of chemosensory perception of smoke by humans, and seek opportunities to apply it to new or improved products” (R. J. Reynolds, 1989). Less than 1 year later, a Philip Morris presentation summarized: “The continued financial success of our business will rely to an ever increasing degree upon our understanding of the chemical senses and the application of this information in the design of new products” (Philip Morris, 1990).

In one experiment, referenced in an internal letter, researchers affiliated with R. J. Reynolds reported that, regarding taste aversion, naturally occurring S(−) nicotine was 4.5 times more effective than R(+) nicotine. The dose level of S(−), where 50% of tested animals display taste aversion, was three times lower than that of the central stimulant amphetamine. The author of the letter, O. Stuhl, recommended using the results from the conditioned taste aversion tests as a baseline for the screening of other alkaline stereoisomers. While suggesting that the results from S(−) nicotine be used to publicly deny claims of addiction, the scientist recommended using R(+) stereoisomers rather than S(−) nicotine in all newly designed cigarettes. Concluding that this would be an excellent marketing strategy for the manufacturer, he reassured others that “the availability of R(+) nicotine is no problem

anymore since the microbiological transformation of S(−) nicotine to R(+) nicotine…-can be accomplished in pilot plant scale which would mean an output of several kg of R(+) nicotine per day" (Stuhl, 1984).

Sensory research was considered with regard to optimal targeting of different consumer subpopulations. For example, an R. J. Reynolds report in the late 1980s indicated that olfactory, trigeminal, and taste sensitivity decline with age. The author suggested that declining taste sensitivity could be correlated to product attributes, and thus, attention should be given to providing a more highly flavored product for the older market and a blander product for the younger aged smoker. The manufacturer sought to specify products for older consumers, who "would probably prefer products with higher levels of odorants. The reverse would be true for younger consumers, e.g. consider Marlboro vs. Winston" (R. J. Reynolds, 1987).

The authors of the same report also considered olfaction thresholds with respect to gender. The report noted that smell thresholds were significantly elevated during menstruation in females, resulting in poor odor sensitivity, and that postmenopausal women have decreased smell activity, otherwise known as hyposmia (R. J. Reynolds, 1987). G. Kobal and other researchers affiliated with Philip Morris also were interested in olfactory sensitivity occurring during a woman's menstrual cycle. Preliminary results from an internal correspondence indicated that sensitivity to some tested odorants varied with changes in the menstrual cycle (Gullotta, 1990a). This and similar research reflects manufacturers' sensitivity to sensory factors specific to subpopulations of smokers (Ayya, Frijters, & de Wijk, 1994; Carchman & Southwick, 1990).

The relationship between the specific components of smoke and their measured subjective effects also was critical to internal product research efforts. Studies were conducted at Philip Morris to identify potential replacements for the additive coumarin, which had been identified as a carcinogen. A 1990 internal Philip Morris presentation described how evidence from these studies supported the identification of noncoumarin component combinations, which yielded a subjective response equivalent to coumarin. Based on that evidence, the manufacturer formulated and successfully implemented a coumarin replacement flavor (Philip Morris, 1990). A related area of interest was the use of sensory stimulation to provide a bridge between product expectations and smoke delivery. As proposed by a Philip Morris scientist: "We might be able to produce the CNS effects of high delivery cigarettes by leading subjects to believe they [are] smoking high nicotine cigarettes when they [are] actually smoking low nicotine cigarettes. Experiments of this type might have important implications for the marketing of low delivery cigarettes" (Gullotta, 1982). Other studies investigated flavor discrimination of different compounds, with a particular goal of identifying olfactory responses with "feel" (mild irritant) qualities. This work led to the development of specific additives aimed at enhancing both the flavor and physical "feel" of tobacco smoke for Philip Morris (Farnham, 1995), as well as assisting development of a better puff profile characteristics for R. J. Reynolds (Jennings et al., 1991).

Discussion

The tobacco industry conducted and sponsored extensive research intended to gain a greater understanding of the role of sensory nerve activity on smokers' responses to nicotine and tobacco smoke. Central to this research were investigations of the sensory influence of nicotine, nicotine analogs, and other substances, including components of tobacco smoke, on the olfactory and trigeminal nerves. The identification of the functional independence of the two nerve networks, together with the discovery of symmetrical projection of olfactory nerve fibers, showed that flavor perception and physical sensation (smoker-described "kick," "bite," or "impact") shared a complex relationship. This work was applied to the understanding of subjective responses to specific smoke components and other product differences. These internal research efforts, led predominantly by Philip Morris and R. J. Reynolds, support the role of sensory nerve activity in modulating smokers' responses to tobacco smoke and may suggest a basis for the development of conditioned nicotine-related responses.

The contribution of associative learning to nicotine dependence is widely accepted (e.g., West, 2006), and a substantial number of empirical studies, including studies funded by the tobacco industry, have demonstrated the capacity for nicotine to serve as a behavioral reinforcer (e.g., Goldberg et al., 1981). A review of the research conducted internally by the tobacco industry suggests that the industry's interest in sensory research was motivated primarily by opportunities for product development, rather than by the desire to understand the mechanisms of addictive behavior. Nonetheless, the internal findings underscore the strong potential for sensory responses to become conditioned via a classical conditioned stimuli–unconditioned stimuli mechanism (Robinson & Berridge, 2003) or to become motivationally enhanced by nicotine via a nonassociative mechanism (Chaudhri et al., 2006).

A substantial amount of industry research has been conducted in the hopes of developing and marketing products that more successfully maintain or enhance smoker response. For example, internal studies of the respective gustatory preferences and olfactory sensitivities of different age and gender groups resulted from an initial understanding of tobacco's effects on the chemical senses, and allowed manufacturers to look deeper into specific physical differences among consumers. Likewise, Philip Morris's attempts to relate flavor components of preferred brands to salivary responses among smokers reflected internal recognition of the importance of associative learning in the adoption and maintenance of smoking behaviors. Recent published studies have shown how the tobacco industry used its knowledge of sensory characteristics—including quality and strength of taste, irritation and impact, and puffing sensations such as draw effort and mouthful (Carpenter, Ferris Wayne, & Connolly, 2006)—to enhance product appeal. These very tangible effects of smoking clearly influence smoker preference (Carpenter et al., 2006; Cook et al., 2003) and were chosen by the tobacco industry as factors that could be readily manipulated to enhance the consumer's experience of smoking.

Internal documents describe manufacturer research on neural and sensory effects and subsequent product design and thus provide critical insight into tobacco product function. One area in which the study of neural mechanisms and sensory impact may prove significant

is in the evaluation of so-called potential reduced exposure products (PREPs), which include denicotinized and reduced toxicant delivery cigarettes. Relatively little is known about the design and delivery mechanisms of these next-generation products and how they differ from conventional cigarettes. Evaluation of potential multiple factors influencing their use—such as design modification, their sensory impact, and consumer acceptance—is warranted, in addition to evaluation of toxin exposure and health outcomes. Sensory research and understanding of peripheral neural responses may be necessary to fully understand smoking topography and other behavioral measures, as well as to gauge market success. A more thorough study of nicotine analogs and their use in development of PREPs may further enhance these aims.

The biological mechanisms elucidated by manufacturers in internal research provide information on a potential psychophysiological basis for non-nicotine effects in nicotine dependence. By modifying the sensory qualities of tobacco products, learned associations might more readily develop to the centrally rewarding effects of nicotine. Such “improved” sensory qualities might contribute to even more rewarding and dependence-forming products. These findings also might suggest new avenues for clinical research and for the continuing advancement of cessation and treatment efforts for dependent behaviors. These internal industry findings also may have implications for policy and could guide the development of more effective treatment strategies, including more “acceptable” nicotine replacement therapies. Had manufacturers been forthcoming with their data regarding the role of olfactory and trigeminal stimulation in forming smoking behaviors and, further, in their ability to manipulate this stimulation through development and application of additives and analogs, regulation and treatment efforts might have been more effective in addressing smoking initiation and targeting of specific smoker groups.

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Table 1.

Initial search terms used to identify relevant industry documents.

Sensory perception, sensory cues, sensory stimulation, sensory effects, sensory properties
Smoking behavior, puffing behavior, olfactometer, respiration, PREP, puff profile, product design
Operant conditioning, classical conditioning, associative learning, learned response, Pavlov, Pavlovian
Cue, reinforcer, CS, US, motivation, lever press, sensitization, drug wanting, drug liking
Olfactory nerve, trigeminal nerve, olfactory bulb, cranial nerve, glossopharyngeal nerve, vagal nerve
Central nervous system, CNS, peripheral effect, anosmic, transection, trigeminal chemoreceptors
Irritant, irritation, nasal, mouth coding, mouth feel, throat, laryngeal
Nicotine analog, capsaicin, nicotinic receptors, acetylcholine, ACh

Table 2.

Selected internal research studies.

Study name	Goal	Measurement techniques	Results
	Trigeminal nerve		
Nicotine-induced EEG and behavioral arousal (Yamamoto & Domino, 1965; for Council for Tobacco Research)	(+) Nicotine base and a variety of other drugs were administered to cats over a 1-min period to test transient behavioral arousal and electroencephalographic activation	Chronically indwelling brain electrodes placed in cats; EEGs recorded and behavior of the sleeping cat analyzed	"The behavior arousal EEG desynchronizing effects of nicotine are due primarily to an action on the CNS rather than peripheral efferent stimulation or release of various neurohormones. However, these latter effects contribute to the total phenomenon produced by nicotine in intact animals"
Nasal trigeminal chemoreception of aliphatic alcohols (R. J. Reynolds, 1984)	To determine the trigeminal system's sensitivity to 8-n aliphatic alcohols	Recordings taken from the ethmoid branch of the rat trigeminal nerve; stimuli presented with an air dilution olfactometer	Response thresholds decreased with increased carbon chain length. "Increasing lipophilicity results in an increasing stimulus effectiveness"
Physiology of trigeminal chemoreceptors in the nasal cavity (Silver, 1988; for R. J. Reynolds)	Trigeminal responses to nicotine, amyl acetate, and toluene measured in rats to examine trigeminal chemoreception in the nasal cavity	Effect of stimulus on respiration measured using an olfactometer; "leaky" integrator used to measure electrophysiological responses to stimuli	Nicotine is slowest to return to baseline levels once the stimulus ceased and proved to be "the most effective trigeminal stimulus and perhaps the most irritating." Trigeminal nerve can be stimulated without causing respiratory change.
	Olfactory nerve		
Olfactory and nonolfactory odor detection in pigeons (Walker et al., 1986; for R. J. Reynolds)	Compared pigeon's sensitivity to four odors before and after resection of the olfactory nerves to discover the interaction between the human olfactory and trigeminal systems	Cardiac conditioning, electroencephalogram, necropsy	"Pre-operative performance at concentrations near threshold was mediated solely by the olfactory system, and post-operative performance was mediated primarily by nasal and ocular receptors of the trigeminal system." Thus, to these stimuli, the olfactory system is more sensitive than the trigeminal system.
Responses recorded from the frog olfactory epithelium after stimulation with R(+) and S(−) nicotine (Kobal et al., 1994; for Phillip Morris)	To determine whether the olfactory system is responsible for the discrimination of stereoisomers of nicotine in frogs	Five measures of four concentrations of distilled R(+) and S(−) and undistilled S(−)-nicotine applied to frogs and EOGs from olfactory epithelium recorded following stimulation; UV detection method used to compare EOGs	Responses to distilled R(+) and S(−) nicotine were significantly higher than to undistilled S(−) nicotine. No significant differences between distilled R(+) and S(−). "Stereospecific perception of the stereoisomers of nicotine in man is probably not mediated by the olfactory system, given that no difference could be found for the measured EOG parameters, suggesting it is mediated by the trigeminal system."

Note. CNS, central nervous system; EEG, electroencephalogram; EOG, electroolfactogram.