A method of naturalistic smoke delivery for use in functional MRI: the MR Hookah

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Abstract

Prior studies using functional MRI (fMRI) to examine the effects of smoking in the brain have necessarily relied on smoking before the MRI exam. We have developed an apparatus (the MR "hookah") for the delivery of cigarette smoke during fMRI exams that mimics much of the process of naturalistic smoking. In this report, we describe the device and characterize its performance in terms of carving reduction and physiological markers of smoke delivery, including change in plasma nicotine and exhaled carbon monoxide, and we contrast the effects of smoking conventional cigarettes to those obtained using specially prepared low nicotine (J2) cigarettes.

Our results on ten individuals indicate that the hookah reduced the urge to smoke and increased plasma nicotine and expired carbon monoxide. Further, while the J2 cigarettes resulted in smaller increases in plasma nicotine, they delivered reductions in cigarette craving that were comparable to the effects of commercial cigarettes. Comparing these data to a control study in which subjects smoked in a conventional manner, our hookah device delivered less nicotine and was overall less effective in craving reduction. A technical evaluation of the device suggests some means by which we might be able to enhance its nicotine delivery.

Overall, these data show that the hookah is an effective means of cigarette smoke delivery that can be used *during* the fMRI exam, allowing physiological studies of the dynamics of brain activation during smoking.

Introduction

Tobacco dependence through cigarette smoking is a brutal problem worldwide. Based on the demographics of its use, and on the plethora of data indicating its serious negative health consequences, one is led to conclude that a substance delivered by cigarettes is among the most addictive known. But what is the substance? While the consensus among researchers is that nicotine is the primary addictive component (Jarvik, 1973; United States Department of Health and Human Services, 1988), there is little evidence of nicotine abuse *per se*. Popular and effective nicotine replacement therapies, such as the nicotine patch, deliver nicotine to reduce cigarette craving and other withdrawal symptoms associated with smoking cessation, but after they have stopped smoking, patients are relatively easily weaned from the nicotine. Nicotine patches and gum do not reduce craving to the same degree as does smoking a customary cigarette (Fiore et al., 1994; Schneider et al., 1984). They also generally do not produce analogous blood levels or peak (bolus) delivery of nicotine to the brain (Benowitz et al., 1990). Cigarettes deliver a veritable cocktail of physiologically active substances and flavorings; they reduce the oxygen content of the inspired air; they deliver particulates that interfere with pulmonary function; and they offer a set of conditioned rewards based on their usual context. These, and many other lines of evidence, indicate that smoking is not simply a vehicle for delivering nicotine, but that other features of the smoking experience contribute to its addictive potential (Rose et al., 2003).

One path to understanding the process of drug-induced reward might be to examine the brain's response to receiving the rewarding substance. Using functional MRI (fMRI), several successful studies have shown activation of classical reward circuitry in human subjects after administration of common drugs of abuse, including cocaine (Breiter and Rosen, 1999; Gollub, 1998; London et al., 1999; Wexler et al., 2001). Others have used fMRI to show altered patterns of brain activity to cognitive challenge in substance abusers as compared to control subjects (Paulus et al., 2002). These experiments exploit the power of fMRI to highlight circuits within the brain that might be associated with problems of abuse.

Significant findings, such as the demonstration of a potential common mechanism of dependence to cocaine and nicotine (Pich et al., 1997) and a decrease in endogenous brain reward during nicotine withdrawal (Epping-Jordan et al., 1998) continue to be obtained from this work. In a series of neuroimaging studies, Stein and colleagues have observed brain signal changes following intravenous injection of nicotine (Bloom et al., 1999; Stein, 2001; Stein et al., 1998). The latter studies successfully simulated some of the cognitive and physiological effects of cigarette smoking, including subjective effects described by the research participants as a "rush" and/or "high" (Stein et al., 1998) and demonstrated activation of a network of brain regions, including cingulate cortex, inferior, medial and superior frontal gyri, insular cortex, angular gyrus and cuneus, as well as subcortical structures: amygdala, thalamus and nucleus accumbens (Bloom et al., 1999; Stein et al., 1998). While these results stand well on their own, they clearly cannot capture all of the components that give cigarettes their rewarding qualities. Although IV nicotine mimics closely the pharmacokinetics of smoking, Westman, *et al.* (Westman et al., 1996) found that, compared to cigarette smoking, experienced smokers reported IV nicotine to be less relaxing, less calming, less satisfying, and less able to reduce craving. Our goal, in the experiments presented here, was to develop a means of delivering cigarette smoke that duplicated as much as possible the experience of cigarette smoking, but offered as well the possibility of controlled delivery of smoke and odorants, and was generally consistent with use in the somewhat inhospitable environment of the magnetic resonance imaging instrument.

In this paper, we report our non-imaging findings using our MRI "hookah", including its ability to reduce craving and to produce physiologically relevant changes including blood nicotine and expired carbon monoxide. We compare our results with the hookah in each of these measures using standard cigarettes and with specially-prepared low nicotine cigarettes, and with both cigarette types smoked conventionally.

METHODS

THE MR HOOKAH

To be fully compatible with our experimental goals it was necessary to create an apparatus for cigarette smoke delivery that 1) creates no artifacts into the MR images, through the introduction of devices or materials that might perturb the magnetic or radio fields 2) allows the subject to inhale and exhale both smoke and room air at his or her own pace 3) allows the smoker to breathe through either nose or mouth 4) quickly removes smoke and excess odorants, so that these potential secondary reinforcers may be controlled in subsequent experiments 5) allows for delivery of experimenter-controlled amounts (doses) of cigarette smoke 6) alters the cigarette flavor as little as possible.

Apparatus

Our device (figure 1, A & B) delivers smoke to the subject through a close fitting silastic® (Dow Corning) mask that includes a mouthpiece that the subject places comfortably in their teeth. Using a standard surgical oxygen mask ensures that the participants are able to breathe through both nose and mouth. We scavenged expired smoke through a low velocity vacuum system that drew air continuously through a large bore tube fitted concentrically around the smoke delivery tube. When the subject was not inhaling cigarette smoke, one-way valve ports on the side of the mask passed room air freely. In this manner the smoke odor, which might act as a secondary reinforcer, and therefore a contaminant in future experiments, was removed from the environment as quickly as possible. To deliver cigarette smoke, the investigator drew smoke from the cigarette using a 100-cc glass syringe fitted to a cigarette holder, all of which activity took place inside a tightly sealed Plexiglas box. We then injected the contents of the syringe into the facemask through a 2-m long plastic tube of 5/16" diameter. The experimenter was able alternate rapidly between drawing smoke from the cigarettes and administering it to the subject.

[Insert figures 1A and 1B about here]

SMOKING MATERIALS

Subjects smoked either their own cigarette brand (average nicotine 1.1 mg) or reduced nicotine "J2" cigarettes supplied for this research by Philip Morris (Richmond, VA). The J2 cigarettes are unflavored and contain tobacco that has been subjected to an extraction process that reduces the nicotine to 0.08 mg (per the manufacturer's labeling), while keeping the tar at levels comparable to conventional cigarettes (9.1 mg). Because of the processing of the J2 cigarettes and their lack of extra flavorings, the taste was not strictly comparable to the subject's regular brand. It is not possible with current technologies to make nicotine-free cigarettes. Throughout this report we refer to the reduced nicotine cigarettes as "NIC–" and the subject's own brand as "NIC+."

SUBJECTS

All subjects, in all experiments, participated under a protocol approved by the UCLA Office for the Protection of Research Subjects and were recruited from the Los Angeles area via printed advertisements and flyers. For inclusion in this study we required that our subjects were smokers in good general health and used no tobacco products other than cigarettes or medications known to affect cognitive functioning. We used a standardized questionnaire to assess neurological health – none of the subjects had a history of neurological abnormality. Subjects participating in experiment 1 were also free of radiological abnormalities as reviewed by MSC.

BEHAVIORAL INSTRUMENTS AND QUESTIONNAIRES:

After obtaining informed consent, the subjects filled in a smoking history a Fagerström Test for Nicotine Dependence questionnaire (Heatherton et al., 1991) and the Edinburgh handedness inventory (Oldfield, 1971). Subjects rated their craving and urge to smoke on three questionnaires. The ten item Urge To Smoke (UTS) scale (Jarvik et al., 2000) was presented as a visual analog scale. The SSI and the Shiffman/Jarvik craving and withdrawal scale (Shiffman and Jarvik, 1976) also were collected in a minority of subjects; these will not be discussed further.

Experiment 1: Hookah Data Collection

Subjects. Ten healthy volunteers (five male), all heavy smokers, were studied in Experiment 1. Participants ranged in age from 18 to 47 years (mean = 29.7, SD=10.5) with smoking histories ranging from 3 to 20 years (mean=10.6, SD=7.1) and average current use of 19 cigarettes per day (range=10-27, SD=4.4). Subjects participated in two experimental sessions and were instructed to remain abstinent for 16 hours prior to each.

Pre-training. The subjects were informed that smoking through the device would be different than customary smoking and thus were pre-trained to smoke on a mock hookah system outside the scanner. They were instructed to take in as much or as little smoke as they wanted. Initially, subjects were given 80 cc of smoke from their own cigarette. A tap on the foot was used to prepare the subjects for the upcoming puff. A total of ten puffs were delivered 30 seconds apart. After each puff subjects were asked if they preferred *more*, *less*, or *the same amount* of smoke, and the volume was adjusted appropriately. Subjects then completed a 100 mm visual analog scale assessing the "harshness", "satisfaction", "pleasure" and "similarity to smoking a regular cigarette" for each puff. Following the pre-training, subjects were given the opportunity to smoke to satiety (for most subjects, the pre-training alone was sufficient for them to reach satiety). Craving was then measured using the Urge to Smoke Scale (UTS)

(Jarvik et al., 2000). At this time an expired carbon monoxide (CO) sample was obtained (Bedfont Micro III Smokerlyzer, United Kingdom) and the subjects were instructed to smoke no more cigarettes until they were asked to do so by the experimenter upon their return to the lab.

Protocol. The morning following pre-training (after 16 hours), the subjects returned to our lab. Abstinence was confirmed by comparing expired CO after the abstinent period to that measured in satiety. Where subjects' CO was 40 ppm or higher the night before, abstinence was considered confirmed if it decreased overnight to 20% or less of the previously measured value (Benowitz 1980; Jarvis 1983). Otherwise, abstinence was confirmed by an expired CO sample of $\leq$ 7 ppm. Following abstinence verification subjects completed the UTS, were catheterized in the antecubital vein or hand of their non-dominant upper extremity, and had their blood drawn (see below).

Blood samples and UTS scores were obtained in abstinence. Subjects then were positioned in the MR scanner and equipped with the hookah's silastic mask and mouthpiece. We delivered puffs of smoke using the same protocol as their pre-training session with the puff volume adjusted accordingly. In one session, subjects were given smoke from their own, conventional NIC+ cigarette. In the other session, subjects were given smoke from NIC– cigarettes. Subjects and experimenters were blinded to which cigarette (NIC+ or NIC–) was used. Blood samples were drawn two minutes after the completion of smoking in the scanner via catheter; at this time, the venous blood nicotine levels are typically plateaued near their peak (Henningfield et al., 1990).

The subjects rated their post-smoking craving through the device on a computerized version of the UTS, presented through MRI compatible goggles (Resonance Technology, Northridge, CA). Accompanying blood samples were collected 2 minutes after smoking through the device, and expired CO samples were levels collected immediately after scanning.

Experiment 2: Normative Data Collection

Subjects. Participants for these experiments were nine heavy smokers between the ages of 23 and 53 years (mean = 30.8, SD=9.7) with smoking histories ranging from 3 to 15 years (mean=8.4, SD=3.6) and current use of 17 cigarettes per day (range=15-20, SD=2.2).

Protocol. Subjects participated in two experimental sessions and were instructed to remain abstinent for sixteen hours prior to each. Abstinence was confirmed using the same criteria as above. Blood samples and UTS scores were obtained in abstinence. In one session, subjects smoked their own, conventional cigarette (NIC+). In another session, subjects were given a NIC– cigarette (see above). Blood samples were collected 2 minutes after smoking; UTS scores and expired CO measures were obtained immediately thereafter.

Blood Collection and Analyses (Experiments 1 and 2)

Blood samples were collected after 16 h of overnight abstinence. In some cases blood draws were delayed as a result of problems with the stability of the catheter. The blood plasma samples were frozen and stored in polyurethane tubes. These samples were analyzed chromatographically for nicotine and cotinine content. This method is capable of resolving levels to a precision of 1 ng/ml in human blood (Jarvis et al., 1987).

Experiment 3: Nicotine Delivery

The nicotine content of the delivered cigarette smoke was assessed for four conditions: NIC+, NIC–, NIC+ cigarette smoke passed through the hookah, and NIC– cigarette smoke passed through the hookah. Ten puffs of smoke were passed through a Cambridge filter using the same smoke delivery protocol outlined above. Three samples were collected for each condition.

For quantification of the deposited nicotine nicotine was extracted from each filter by adding 6 mL of 0.01M HCl in a Petri dish to soak the filter. Next, the filter was placed inside the syringe, and the solution was drawn into the syringe 3 more times to complete the washing process. The solution was expelled from the syringe and the weight of the 0.01M HCl was recorded. The concentration of nicotine (ng/mL) in the solute was established, and multiplied by the amount of 0.01M HCl obtained after the washing process.

RESULTS

Experiment 1: Hookah

We excluded 7, 8 and 10 of the UTS scale, as they contained double negatives and confused some subjects. We calculated change scores (Δ) for each item and each subject and treated these as separate measures of craving. Craving was calculated in the same way for subjects who smoked through the hookah and for normative subjects. The UTS was lowered when subjects were delivered NIC+ smoke from their own cigarettes (paired t-test, N = 10, $p<0.0001$, Mean $\Delta = 1.4$, SD = 2.0). The reduction in UTS was significant also when subjects were delivered NIC– smoke (N = 9, $p < 0.0001$, Mean $\Delta = 1.3$, SD = 1.6). This change did not differ significantly between the two conditions.

Smoking the NIC+ cigarettes resulted in a 3.1 ng/ml, increase in blood plasma nicotine (N=7, $p < 0.05$, SD = 1.1 ng/ml), while the increase in plasma nicotine was not significant when subjects were delivered smoke from NIC– cigarettes (N = 5, $p > 0.1$, Mean $\Delta = 0.4$ ng/ml, SD = 1.1 ng/ml). The subject's expired CO increased by 3.0 ppm (SD = 3.2 ppm) by either the NIC– (N=6, $p<0.01$) and NIC+ (N=5, $p<0.01$) cigarettes; this CO increase did not differ detectably by cigarette type.

Experiment 2: Normative Smoking

The measured UTS was lowered when subjects smoked NIC+ cigarettes (N=9, $p < 0.0001$, Mean $\Delta = 2.4$, SD = 1.9); it also was reduced when subjects smoked NIC– cigarettes (N=9, $p<0.0001$, Mean $\Delta = 2.9$, SD = 1.7). The subjects experienced *greater* craving reduction when they smoked NIC– cigarettes than when they smoked NIC+ cigarettes (N=9, $p=0.1$).

Blood plasma nicotine was boosted when subjects smoked their own cigarette normally (N=9, $p=0.0001$, Mean Δ = 9.7 ng/ml, SD = 4.6 ng/ml). The increase in plasma nicotine was not significant when subjects smoked NIC– cigarettes, even though subjects reported significant reductions in craving immediately after smoking these cigarettes (N= 8, $p < 0.01$, Mean Δ = 0.64 ng/ml, SD= 1.9 ng/ml). Expired CO was increased after smoking NIC+ cigarettes (N = 9, $p < 0.0001$, Mean Δ = 3.2 ppm, SD = 1.6 ppm). The CO increases did not differ between NIC– and NIC+ cigarettes (N = 9, $p < 0.0001$, Mean Δ = 3.4 ppm, SD = 1.3 ppm).

Normative vs. Hookah smoke administration

These experiments allowed us to make several comparisons between the results of smoke delivery by the MRI hookah and by normal cigarette smoking.

Increases in CO were not different between the two means of smoke administration, whether the subjects smoked NIC+ or NIC– cigarettes. On its own, this suggests that the total smoke delivery probably did not differ greatly. Compared to our normative results, UTS reduction was significantly lower when subjects smoked through the hookah. This was true when subjects smoked NIC+ ($p < 0.0001$) or NIC– cigarettes ($p < 0.0001$). The increase in plasma nicotine was approximately 3 times greater when the subjects smoked their own cigarettes conventionally than when they smoked them through the hookah. Though the mean increase in nicotine after using NIC– was lower in the hookah than by normal smoking, the difference wasn't significant. Notably, however, both were very low. Figures 3 and 4 summarize the experimental results for all smoking conditions.

[Insert Figure 3 and 4 about here]

Experiment 3: Nicotine Delivery

Having observed that the hookah delivered about 3-fold less nicotine, even though the CO increases were similar we set out to determine the reason for its decreased efficiency. We hypothesized that the amount of nicotine in normal cigarette smoke was reduced by the smoke's passage through the tubing rather than reduced smoke delivery by the experimenter. To test this, we measured the amount of nicotine contained by smoke when smoke either did or did not pass through the hookah's tubing. Smoke that was passed through Cambridge Filters contained three times less nicotine if it first traveled through the hookah's tubing than when it did not ($p < 0.01$, 0.23 mg/ filter vs. 0.66 mg/filter).

DISCUSSION

The MR hookah mimics the delivery of many components of conventional cigarette smoking, including a reduction in craving, and increased blood nicotine, as well as less tangible, but still important factors such as the experience of smoke inhalation, and the distinctive taste of cigarettes that are likely to be important secondary reinforcers. Our own data show that smokers achieve a high degree of craving reduction even from cigarettes with low or insignificant levels of nicotine. Studies of abstinent smokers have consistently found that denicotinized cigarettes reduce craving (Butschky et al., 1995; Westman et al., 1996). Nicotine-containing and denicotinized cigarettes have been found equally able to delay the onset of withdrawal (Gross et al., 1997) and relieve acute withdrawal symptoms (Butschky et al., 1995; Westman et al., 1996). Though this change in craving may be short-lived, it underlines the significance of the complex components of cigarette smoke on the behavior and its reinforcement.

The quantitative effects of the hookah on both craving reduction and nicotine delivery were significantly smaller than those achieved when cigarettes were smoked normally. One likely explanation (Gerd Kobal, was that nicotine evaporated off of the smoke particles and condensed on the approximately 2 m tube that separated the smoke delivery box from the subject, resulting in a reduced net delivery (Lipowicz and Piade, 2004). Our separate series of experiments on the effects of tubing length strongly support this theory. They also point to a potential solution: the delivery tubes could be heated to a critical temperature high enough to keep the nicotine vaporized. In fact, this temperature control might provide an independent means of controlling the nicotine dose, while still using the subject's preferred cigarette brand.

The aforementioned limitations notwithstanding, we contend that we have created and characterized a practical means of administering cigarette smoke in a mode that is naturalistic but still consistent with

the requirement for subjects to remain still in the scanner[1] and unable to use their own hand to move the cigarette to their mouth.

While the smoking device meets many of our original objectives, it is worth noting that it may fall short in others ways. In particular, there is no normal tactile feedback (e.g., the repetitive motion of moving the cigarette to and from the mouth); the smoke flavor is almost certainly at least slightly altered. It is likely too, that in most experimental designs likely to use this device (for example, those that follow), the rate of smoke delivery is under the control of the experimenter, and not truly *ad libitum*, as might be the case for truly naturalistic smoking.

[1] This, despite the fact that they are usually admonished not to smoke in bed

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TABLES

HOOKAH	NIC+	NIC–	NIC+ vs. NIC–
UTS	- 1.4 ± 2.0	- 1.3 ± 1.6	n.s.
Plasma Nicotine	+ 3.1 ± 1.1 ng/ml	+0.4 ± 1.1 ng/ml	n.s.
Expired CO	+ 3.0 ± 3.2 ppm	+ 3.0 ± 3.2 ppm	n.s.

NORMATIVE	NIC+	NIC–	NIC+ vs. NIC–
UTS	- 2.4 ± 1.9	- 2.9 ± 1.7	$p < 0.05$
Plasma Nicotine	+ 9.7 ± 4.6 ng/ml	+.64 ± 1.9 ng/ml	$p < 0.0001$
Expired CO	+ 3.2 ± 1.6 ppm	+ 3.4 ± 1.3 ppm	n.s.

Table 1. Summary of results from smoke delivery by the hookah (top) and conventionally (bottom).

FIGURE CAPTIONS

Figure 1A.

Schematic representation of the smoke delivery system. The experimenter draws smoke into a 100 cc glass syringe and can redirect it to the subject in controlled doses through the a 1.5 m plastic tube.

Figure 1B

Schematic of the fully enclosed and continuously vented cigarette "puffing" apparatus. The face mask used by the subject to inhale cigarette smoke. The smoke is delivered through the center cannula of a concentric dual hose apparatus and the expired smoke is exhausted through the outer tube into the fully contained smoke-delivery box of figure 1A.

Figure 2.

Smoking apparatus as it appears in use.

Figure 3.

UTS Scores Before and After Smoking. UTS Scores ± s.e.m. for NIC+ and NIC– cigarettes smoked through the MR hookah (left) and under normal conditions (right). The UTS decreases did not differ significantly for NIC+ and NIC– cigarettes, but were of greater magnitude for cigarettes consumed in standard conditions than through the MR hookah.

Figure 4.

Plasma Nicotine Before and After Smoking. Nicotine Concentratiaon (ng/ml ± s.e.m.) for NIC+ and NIC– cigarettes smoked through the MR hookah (left) and under normal conditions (right).