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Smoking and Neuroimaging: A Review

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Abstract

Cigarette smoking is a significant public health concern, often resulting in nicotine dependence, a chronic-relapsing psychiatric diagnosis that is responsible for up to 10% of the global cardiovascular disease burden. Due to its significantly deleterious effects on health, much research has been dedicated to elucidating the underlying neurobiology of smoking. This brief article is intended to provide a digestible synopsis of the considerable research being conducted on the underlying neural bases of cigarette smoking and nicotine dependence, especially for cardiologists who are often at the front lines of treating nicotine dependence. To this end, we first review some of the most common neuroimaging methodologies used in the study of smoking, as well as the most recent findings from this exciting area of research. Then, we focus on several fundamental topics including the acute pharmacological effects, acute neurocognitive effects, and the long-term neurobiological effects associated with smoking. We finally review recent findings regarding the neuropsychological processes associated with smoking cessation, including cue-induced craving and regulation of craving. Research in this field beginning to uncover how some of these neuropsychological processes are similar across clinical disorders which cardiologists also encounter frequently, such as craving for food resulting in overeating. We conclude with recommendations for future neuroimaging work on these topics.

Keywords

Smoking; cigarettes; nicotine; tobacco; fMRI; PET; SPECT; neuroimaging; acute effects; long term effects; cognition; pharmacokinetics; craving; dopamine; nicotinic acetylcholine receptor; nAChR; pharmacology; psychomotor stilmulant

Introduction

Cigarette smoking is routinely associated with unfavorable outcomes such as premature death from chronic diseases, a substantial burden on health-care systems, and economic losses to society. In the United States alone, over 443,000 deaths are attributable to cigarette smoking every year, making it the leading preventable cause of disease and death and a major cause of preventable cardiovascular morbidity and mortality in particular [1]. Measured in terms of the burden on services such as health-care and law enforcement, the loss of productivity in the home or workplace, and premature death and disability, the yearly estimated costs of cigarette smoking in the United States exceed $193 billion [2]. For comparison, this figure is greater than the Gross Domestic Product of nations including Finland ($188 billion) and Ireland ($181 billion; according to the World Bank). Despite these grim statistics as well as the personal economic burden of smoking (the cost of a pack of cigarettes exceeds $12 in some cities), 43.4 million of US adults smoke cigarettes and nearly 34 million of them are daily smokers [1]. Given its prevalence and negative

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outcomes, cigarette smoking represents a crucial field of study, and a focus of clinical intervention. Cardiologists, who are often at the front line of treating nicotine dependence, may be interested in the complex neural processes underlying smoking and smoking-induced neural change.

In this review, we first briefly survey imaging methodologies that have been used to study smoking as well as other clinical disorders that cardiologists need to address as part of comprehensive treatment programs (e.g., obesity, depression, and stress). Then, we focus on several questions that recent work has addressed regarding the underlying neurobiology of this behavior. Namely, what are the acute pharmacological effects of smoking and nicotine administration? What are the acute neurocognitive effects? What are the long-term effects? Finally, we review recent findings on psychological processes associated with nicotine dependence and treatment.

Neuroimaging Tools

Several neuroimaging methodologies have been used to inform our understanding of the pharmacological, neurocognitive, and psychological effects of cigarette smoking. As will be detailed below, each neuroimaging tool can be used to understand only *some* aspects of these processes. Therefore, the kind of data generated by each study crucially depends on the *type* of imaging methodology, in addition to study design and analysis techniques. Together, these factors limit both the kinds of questions that can be asked, as well as the answers each study can provide.

PET and SPECT

Positron Emission Tomography is a common functional neuroimaging technique. A short-lived radioactive isotope is incorporated into a biologically active molecule, such as glucose. The radioactive tracer is then injected or infused into a living subject. As the tracer decays, the PET system detects pairs of gamma rays that are indirectly emitted in the process, and uses them to localize the tracer to a particular region in the brain. In this way, the concentration of tracer molecules can be estimated at different locations in the brain or other tissue. Single Photon Emission Computed Tomography also uses radioactive tracers incorporated into active biological molecules. However, SPECT tracer molecules are different than PET in that they directly emit a single gamma ray during decay. The nature of the signal allows for lower resolution images than PET; however, SPECT tracers typically have a longer half-life and the scans are more easily executed. Nevertheless, both methods can probe several aspects of brain function rather than structure. Depending on the tracer used, PET and SPECT data can indicate regional brain activity (e.g., via glucose metabolism when the tracer is a modified sugar, as in ^{18}F-fluorodeoxyglucose) or receptor occupancy (e.g., with ^{11}C-raclopride and dopamine receptors) and pharmacokinetics, when multiple measurements are taken after drug consumption.

Structural MRI

Magnetic Resonance Imaging scanners use strong magnetic fields to align the magnetization of hydrogen nuclei in water molecules in the brain. Radio frequencies are then used to systematically alter the alignment of this magnetization, slice by slice, so the scanner can measure the resulting rotating field of the atomic nuclei. Importantly, different kinds of tissue (e.g., white matter, gray matter) exhibit different magnetic properties, and can be differentiated based on the density of detected protons. This allows for different kinds of 3D images to be constructed. Other MRI techniques can be used to investigate specific aspects of brain structure, such as the relative integrity of white matter tracts. For example, diffusion tensor imaging (DTI) measures the movement of water molecules along axonal tracts,

creating a 3D map of white matter connectivity. However, relatively little work has used this tool to investigate the effects of cigarette smoking, and it is therefore not reviewed herein.

Functional MRI

While structural and functional MRI are measured in the same scanner, the imaging contrast (T2*) used for fMRI capitalizes on the fact that oxygenated and deoxygenated blood have different magnetic properties. This allows the measurement of the Blood Oxygen Level Dependent (BOLD) signal, which serves as a proxy for brain activity. Importantly, the BOLD measurement is estimated *relative* to a baseline. Therefore, the BOLD signal in any measured condition (after smoking) is typically contrasted from activity in another condition (before smoking), to isolate a process of interest (e.g., smoking). Conversely, the Arterial Spin Labeling (ASL) method uses the same MRI machinery to obtain a measure of absolute perfusion, rather than relative blood flow. It typically does so by comparing two images, one collected after using 180-degree radiofrequency pulse, which magnetically 'labels' water molecules in the blood. Finally, in recent years, fMRI-tracer methods have been developed that increase contrast, but those are infrequently used, as they are more invasive.

Taken together, neuroimaging methodologies can answer questions regarding brain structure (MRI), different aspects of brain function (PET, SPECT, fMRI, and ASL), and pharmacokinetics (PET, SPECT) in animals as well as humans.

Neuroimaging Study Designs

Each of the methodologies reviewed above lends itself to specific study designs. For functional studies, one typical design compares neural activity following nicotine vs. placebo administration, to isolate the acute effects of the drug. Although cigarette smoking is often the behavior of interest in such studies, and cigarettes contain many other compounds, nicotine is considered the primary pharmacological agent. As such, nicotine – in cigarettes, inhalers, or nicotine gum – is often the focus of the available neuroimaging work.

Following the administration of nicotine, functional neuroimaging studies can directly investigate pharmacological effects as well as changes in neural activity during performance of various cognitive tasks. The exact nature of the generated data depends on the specific method used (fMRI/ASL/PET/SPECT; documenting drug-induced changes in blood flow, perfusion, metabolism of a radioactively-labeled molecule, or receptor occupancy). Overall, findings from functional studies provide invaluable information about how global or regional neural activity changes as a function of drug administration and suggest mechanistic relationships between neural activity and smoking. However, as will be discussed below, without commensurate changes in subjective effects, clinical markers, cognitive task performance, or behavior, some findings may be difficult to interpret.

On the other hand, structural studies typically compare smokers to non-smokers, in an attempt to evaluate the effects of smoking on cortical thickness or volume. Importantly, however, when such studies are cross-sectional (comparing groups at a single point in time) they cannot definitively attribute differences to cigarette smoking. As such, they are merely suggestive. Indeed, unless studies are longitudinal, we cannot conclude with confidence that any brain differences observed between non-smokers and smokers are caused by smoking (as they may have been pre-existing). Throughout this review, we attempt to relate the specific methodology and study design to the resulting data, and to carefully evaluate the implications of each study to the neurobiology of cigarette smoking.

Acute Pharmacological Effects

It has been known for some time, based on careful animal studies, that nicotine crosses the blood-brain-barrier easily and binds to the nicotinic subtype of acetylcholine receptors (nAChR). These receptors are located on both pre- and post-synaptic membranes of various types of neurons. Further, there are multiple subtypes of nAChRs that exhibit distinct pharmacological and functional properties, and which are distributed globally throughout the brain. These appear in particularly high concentration in the cortex, striatum, cerebellum, thalamus, and limbic regions [3].

Pharmacokinetics

It has been suggested that the pharmacokinetics of smoking have clinical implications for the acquisition of smoking behavior. In an attempt to shed light on this question, neuroimaging studies have investigated the pharmacokinetic process in detail, and begun to relate it to clinical variables. For example, until recently it was thought that brain nicotine concentration rises and falls rapidly following each single puff of a cigarette [4]. However, a recent study used PET and radiolabeled nicotine to demonstrate that while a single puff leads to a rapid rise in brain nicotine concentration, it washes out gradually rather than rapidly [5]. Further, it was recently demonstrated that nicotine accumulation in the brain during smoking of one full cigarette increases in an approximately linear fashion with successive puffs, rather than in puff-associated spikes and rapid washouts. Relating this finding to clinical variables, the authors reported that dependent smokers showed a slower rate of brain nicotine accumulation than non-dependent smokers [4]. While these findings are informative, it is still unclear whether the rate of accumulation changes as individuals transition into dependence, and the extent to which nicotine's pharmacokinetic properties are related to frequency or duration of use.

The putative rise of nicotine concentration in the brain results in nAChR binding, and activation of the receptors. Both PET and SPECT studies have used ligands with nAChR affinity to investigate the neural dynamics of nAChR binding. It was shown that after smoking a single cigarette, $\alpha 4\beta 2^*$ nAChR maximum occupancy reached 88% (averaged across the thalamus, brain stem, and cerebellum; where the * represents a variable subunit [6]). Other studies reported $\beta 2^*$ nAChR occupancy at a maximum of 65-70% after smoking, or use of a nicotine inhaler [7, 8]. In the latter study, degree of receptor occupancy was negatively correlated with reduction in withdrawal symptoms after cigarette smoking, and positively correlated with cigarette craving both before and after the use of a nicotine inhaler [8]. These findings suggest that nicotine consumption leads to pervasive occupancy of nAChR receptors, as well as a direct relationship between occupancy and subjective effects of smoking.

Effects on Dopamine (DA) System

Although there is a clear and crucial role for ACh in mediating the reinforcing effects of nicotine, instrumental responding to nicotine is also supported by dopaminergic activity (for discussion, see [3]). It has been known for some time that nicotine increases DA concentration in the ventral striatum of animals, like other drugs of abuse [9]. Similarly, in human smokers, DA binding in the striatum increases after smoking a cigarette [10] and this effect is dependent on nicotine itself, rather than the act of smoking (measured using PET, [11]). Interestingly, others reported that while smokers show increased striatal DA binding to nicotine gum vs. placebo, non-smokers do not, suggesting that binding is influenced by smoking history. Consistently, binding differences between nicotine and placebo administration correlated with degree of nicotine dependence (i.e., those who were most dependent, showed the greatest relative increases in binding to nicotine gum [12]). These

findings suggest a role for DA in cigarette smoking, although the complex interplay between ACh and DA has yet to be elucidated.

Effects on Blood Flow

Early neuroimaging studies suggested that nicotine administration is associated with decreases in global brain activity (measured by PET, [13, 14]), but increases in regional activity, predominately throughout cortico-basal ganglia-thalamic circuits (across different methodologies, reviewed in [15]). Animal imaging work using MRI and β2 subunit knockout mice suggests that these changes are predominantly mediated by β2* nAChRs [16]. Indeed, it has been argued that the increases in these regions (contrasted with global decreases) are due to the high density of β2* nAChRs receptors [13]. Addressing blood flow changes on a more global level, an emerging line of fMRI work in humans investigates patterns of connectivity between different brain regions during a period of rest (termed 'resting state functional connectivity'). Recent findings suggest that such connectivity may also change in response to nicotine administration [17]. Furthermore, the degree of connectivity within the ' default mode network' (a network that is commonly deactivated during effortful cognitive engagement and more activated during rest) correlates with self reported relief of withdrawal symptoms after abstinence [18]. It is too early to draw conclusions from this work, but relating such neuroimaging findings to clinical symptoms and outcome is a promising direction.

Acute Neurocognitive Effects

Nicotine is a known psychomotor stimulant. A recent meta-analysis of nicotine's effects on cognitive task performance revealed significant and consistent enhancement of fine motor responding, reaction times, and accuracy in both non-smokers and non-deprived smokers [19]. Consistently, nicotine withdrawal is associated with performance deficits in dependent smokers, and smoking reverses these deficits [19]. Neuroimaging studies have investigated the effect of nicotine administration on neural responses during cognitive task performance in an attempt to elucidate the underlying neuropharmacology of nicotine's acute cognitive effects. Unfortunately, at this time there is little consensus among studies, in part due to variable populations, routes of nicotine administration, and the length of pre-testing abstinence in smokers (resulting in variable degrees of withdrawal).

For example, early PET and fMRI studies with cigarette smokers compared neural activity during working memory and attention tasks, following abstinence as well as acute nicotine administration. This work yielded conflicting results – activity increased or decreased following nicotine administration in several brain regions (reviewed in [20]) and results were difficult to interpret in the absence of performance differences. Several recent studies reported reduced activity in task-related regions following smoking, relative to abstinence of variable lengths [20-22]. The authors of these studies suggested that reduced activity after smoking is due to "increased functional efficiency" although they too reported small or no improvements in task performance.

Several fMRI studies with non-smokers reported reductions in task-related brain activity following nicotine administration that also improved attentional reorienting [23, 24]. However, a similar study reported increases in task-related activity concomitant with improved working memory performance [25]. A few recent studies focused on the heterogeneity of neural response to nicotine administration in both smokers and non-smokers. These studies found that individual differences in brain activity predicted task performance [26-28] suggesting that neural responsiveness to nicotine is an important factor in understanding the acute cognitive effects of nicotine and smoking.

Taken together, these functional neuroimaging results are mixed. They suggest that nicotine administration can *alter* neural activity during cognitive tasks, which *may* play a role in task performance. Although recent work on individual differences in nicotine responsiveness may offer new insights on prior null findings, a mechanistic understanding of nicotine's neurocognitive effects has not yet been established. Indeed, in our view, neural differences remain difficult to interpret in the absence of performance differences. Nevertheless, it has been suggested that neuroimaging studies may detect components of cognitive-attentional processing that are simply more subtle than those detected by behavior alone. To address these issues, future studies could directly investigate tasks that are sensitive to nicotine's effects on performance, while accounting for individual differences. In addition, improvements due to nicotine and reversal of withdrawal effects could be further differentiated in studies that compare performance at variable abstinence periods in smokers to non-smokers.

Long Term Effects

Neuroimaging studies have typically investigated the long-term effects of nicotine by comparing smokers to non-smokers in cross-sectional designs. Over the last decade, such studies have identified both structural and functional between-group differences. While such designs cannot tell us definitively about long-term changes in the brain that are caused by cigarette use, they can suggest candidate brain regions likely to be associated with smoking – either as neurobiological risk factors or as sites affected by chronic use. However, when combined with abstinence manipulations, such studies can also reveal the dynamics of nicotine effects and their reversal.

Effects on Nicotine Receptors

One identified between-group difference includes alterations to nicotinic receptor density, which may be increased in dependent smokers. Measured using PET, smokers show a higher density of $\alpha 4\beta 2^*$ nAChR receptors than non-smokers throughout most of the brain [29]. Consistently, SPECT studies also show that $\beta 2^*$ nAChR availability is increased one week into abstinence in the striatum, cerebellum and cortex [30, 31]. However, an elegant study by Cosgrove and colleagues (2009) provides additional insight into the dynamic nature of this process. By scanning participants repeatedly over time, the authors show that receptor availability changes from early to late abstinence, with smokers returning to non-smoking levels of receptor availability by 4-6 weeks [30]. These findings suggest that smoking is associated with increased nAChR availability, but that receptor density can normalize over time when smokers quit.

Effects on Other Systems

Alterations in the dopamine system have also been identified. Using a radiolabeled DA precursor as a PET ligand, catecholamine utilization in the striatum of nicotine-dependent monkeys was reportedly reduced after 8 hours of abstinence. This was reversed with subsequent nicotine administration [32]. Notably, dependence in this study was established after 9 days of repeated administration, suggesting that nicotine-induced adaptations of catecholamine utilization is relatively rapid. In humans, a recent dual-isotope SPECT study concurrently suggested that while striatal availability of the presynaptic dopamine transporter DAT is relatively decreased in non-abstinent smokers, striatal dopamine D2/D3 receptor availability is not different from non-smokers [33]. Perhaps more revealing was the finding that scores on the Fragerström Test of Nicotine Dependence (a common measure of dependence) correlated negatively with DAT availability, suggesting a functional relationship. Very few neuroimaging studies to date have explored the long-term effects of smoking on other neurotransmitter systems, although a recent SPECT study reported no

difference in $GABA_A$-Benzodiazepine receptor availability between abstinent smokers and non-smokers [34].

Finally, as nicotine is only one of over 4000 compounds present in tobacco smoke, some long-term effects of smoking are not mediated by nicotine. For example, tobacco is known to include inhibitors of Monoamine Oxidase (MAO) enzymes, and cigarette smokers show reductions in MAO-A levels that mimic treatment with well-known pharmaceutical anti-depressant MAO inhibitors [35]. These latter findings have been used to suggest a link between cigarette smoking and mood modulation, and a role for smoking as a form of "self-medication."

Effects on Brain Structure

A body of animal literature has previously shown that nicotine decreases cell numbers and increases markers of apoptosis. In humans, the majority of research has been cross sectional, focusing on the differences in the volume or density of neural tissue between smokers and non-smokers. Cigarette smoking has been associated with generalized brain atrophy and other white matter alterations (for review, see [3]). In addition, across studies, gray matter volume and density are decreased in smokers in a number of regions, including several prefrontal regions, cerebellum [36, 37] and other regions implicated in Alzheimer's disease (e.g., [38]). Importantly, several studies reported negative correlations between prefrontal measurements and smoking history, such that heavier smokers had lower prefrontal volume or density [36, 37, 39]. Taken together, these data suggest that cigarette smoking affects brain structure and morphology, although whether these effects are deleterious is not clearly established.

Psychological factors

As noted previously, cigarette smoking is associated with staggering social costs, in part due to high rates of nicotine dependence, which is a chronic, relapsing condition. Among those who try smoking at least once, the risk of becoming dependent is reported at 31.5%, much higher than for cocaine (16.5%) or alcohol (10%) [40]. Once cigarette smokers become dependent, relapse to smoking is the typical outcome of even the best treatments [41]. Consistent with the known deleterious effects of smoking on health, nicotine dependence is thus one of the most fatal psychiatric disorders [42]. Therefore, psychological processes underlying nicotine dependence and its treatment are important to investigate.

One exciting body of neuroimaging work explores the psychological phenomenon of craving. Craving is a complex and multidimensional construct, involving cognitive, affective and motivational components [43]. Craving has been shown to be predictive of relapse across substance use disorders (see [44] for review), and in cigarette smokers in particular [45]. Over the past 15 years, an extensive body of work has examined neural responses during craving. To induce craving, such studies typically expose drug users to cues that were previously associated with drug use (e.g., pictures of drugs and paraphernalia, movies of other using, drug imagery, etc.) A substantial portion of these studies have focused on cigarette cues and the resulting cigarette craving (for review see [46]).

Broadly summarized, these studies implicate the ventral striatum, amygdala, insula, orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex, and posterior cingulate cortex in responding to cigarette cues and in the experience of craving. Notably, these regions share considerable overlap with those previously associated with emotion, valuation, evaluation, and learning. At this time, a meta-analysis would be best-suited to systematically summarize this body of work, in order to identify the regions most consistently associated with craving and to disambiguate sub-components of a potential

system (e.g., [47]). However, such quantitative meta-analytic studies have yet to be published on the topic.

Due to the importance of craving in drug taking, it has been studied in clinical settings as well. Indeed, several interventions are known to reduce craving as well as smoking, including Cognitive Behavioral Therapy (CBT) and pharmacological treatments like Varenicline. In recent years, several fMRI studies have investigated the neural mechanisms that may underlie their effects. For example, in our own work [46] we used fMRI to model a crucial component of CBT: the regulation of craving using cognitive strategies. We showed that when cigarette smokers used a CBT-like cognitive strategy (i.e., “think of the long term consequences associated with smoking”), they recruited a set of prefrontal regions including dorsolateral and ventrolateral prefrontal cortex. This, in turn, was associated with significant decreases in activity in the regions previously associated with craving, as well as significant decreases in the subjective experience of craving. Further, we identified a specific prefrontal region (dorsolateral prefrontal cortex) in which increased activity correlated with decreases in subjective craving – suggesting a potential mechanism for the efficacy of CBT for smoking cessation, and a target for therapeutic interventions at the circuit level.

Franklin and colleagues (2011) used ASL to investigate neural changes associated with Varenicline treatment during the experience of cue-induced craving. Compared to placebo, they showed that 3 weeks of Varenicline treatment attenuated reported craving as well as neural activity in regions associated with craving [48]. Taken together, these findings highlight that reduction in craving and in craving-related neural activity may be central to the mechanism of action of both CBT and pharmacological treatments for cigarette smoking. Future work drawing a link between such modulation of craving and long-term treatment success will significantly improve our understanding of the mechanism by which such treatments may exert their effect, and of treatment-related change.

Finally, several recent studies related neural activity during passive viewing of smoking cessation ads to reduction in smoking over time. For example, a recent fMRI study reported that several regions including medial prefrontal cortex and precuneus were preferentially activated during viewing of anti-smoking messages that were individually tailored (compared to untailored smoking cessation messages). Furthermore, they showed that activity in these regions predicted reduction in smoking at a 4-month follow up [49]. Similarly, another study showed that medial prefrontal activity during viewing of smoking ads predicted smoking outcome 1 month later, above and beyond self-reported intention to quit [50]. Although they are exploratory in nature, these studies set the stage for what may be the next wave of research on smoking cessation: relating neuroimaging data to behavior change.

Conclusions

Cigarette smoking poses serious health risks, including cardiovascular disease, making it an important target of study. Neuroimaging tools have been used to elucidate the acute pharmacological, neurocognitive, and long-term effects of smoking. MRI has been used to identify structural differences between smokers and non-smokers whereas functional methodologies like PET and SPECT have been used to investigate the acute pharmacological effects of nicotine, the effects of abstinence, as well as functional differences between smokers and non-smokers. Recent fMRI work directly investigated neurocognitive effects of smoking as well as mechanisms that may underlie successful treatments for smoking cessation, and related neural activity to smoking behavior over time. Such work is important to understand for cardiologists who are often confronted with nicotine dependence and who may be able to use this knowledge as part of comprehensive treatment programs. Future work may be able to integrate across different levels of analysis

by comparing PET, MRI and fMRI data from a single subject, to assess effects of smoking, and to further relate the findings to past and future smoking behavior in an effort to understand cigarette smoking and its neurobiological underpinnings, with the ultimate hope of improving treatments and increasing patient health.

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