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Neuroimaging of Nicotine Dependence: Key Findings and Application to the Study of Smoking-Mental Illness Comorbidity

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Abstract

Modern neuroimaging techniques offer the opportunity to non-invasively study neuroanatomical and neurofunctional correlates of nicotine dependence and its treatment. In the present review, the most widely used neuroimaging techniques—magnetic resonance imaging (MRI), positron emission tomography (PET) and functional MRI (fMRI)—are briefly described and their strengths and limitations discussed. The use of these techniques has resulted in new insights into the neuropharmacology of tobacco addiction. Studies comparing smokers and nonsmokers have shown that smokers have less grey matter density in frontal brain regions and greater concentrations of nicotinic receptors. Research on the effects of smoking a cigarette confirms that smoking leads to the release of dopamine in brain reward areas and to nicotinic receptor binding. Studies of smoking abstinence have identified functional brain correlates of increased reactivity to smoking-related cues, and worsening of concentration. To date, neuroimaging studies of nicotine dependence among individuals with mental illness have focused almost exclusively on schizophrenia. A conceptual/methodological framework for studying dual diagnosis using neuroimaging measures is provided with the aim of spurring additional research in this area.

Keywords

MRI; fMRI; PET; nicotine; smoking; nicotine dependence; ADHD; schizophrenia; dual diagnosis; comorbidity

Individuals with mental illness smoke at disproportionately high rates (Lasser et al., 2000). While epidemiologic investigations have provided a picture of the breadth and scope of smoking among these individuals, little remains known about the neurobehavioral mechanisms that underlie this comorbidity. The aims of the present paper are to briefly review neuroimaging studies of nicotine dependence—both inside and outside the context of dual-diagnosis—and to provide a conceptual/methodological framework for conducting future research.

Modern human neuroimaging techniques

Technological advances of the last 20 years have afforded the opportunity to investigate brain structure and function in humans with increasing biochemical specificity and spatial resolution (Huettel, Song, & McCarthy, 2004). Positron emission tomography (PET) identifies the location and concentration of biologically relevant compounds that have been labeled with a radioactive isotope and then injected into the subject. Using this methodology, cerebral blood flow, glucose metabolism and neurotransmitter receptor binding can be measured in different patient groups and under varying conditions. As such, PET allows for the study of *in vivo*

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activity of a broad range of compounds, many of which are of interest in addiction/psychiatric research. These compounds include nicotine, receptor specific nicotinic agonists and dopamine agonists.

Magnetic resonance imaging (MRI) uses magnetic fields and radiofrequency energy to detect differences in proton density of different tissue types. The resulting data are relatively high spatial resolution images that differentiate brain tissue types (e.g. grey matter, white matter). This data can be used to quantify and compare the size and shape of brain regions between groups (e.g. smokers vs. controls), or to predict symptom severity or treatment outcomes.

Functional MRI (fMRI) uses the same apparatus as MRI, but can provide near real-time information about changes in brain hemodynamics. Blood oxygen level dependent (BOLD) fMRI provides information about changes in blood flow by detecting changes in regional blood oxygenation levels. These changes in blood flow are inferred as reflecting changes in neural activity in a particular region (Logothetis & Pfeuffer, 2004). BOLD-fMRI provides a measure of relative blood flow, which means that activation must always be contrasted with a nearby control condition. Other variants of fMRI, including arterial spin labeling (ASL), can provide absolute measures of brain blood flow and are increasingly used.

Brief review of key neuroimaging findings

The brain of the smoker

Compared to nonsmokers, smokers have been shown to have reduced grey matter volume and density in prefrontal cortical areas involved in executive function (Brody et al., 2004). Smokers' and nonsmokers' brains have also been shown to differ in the distribution of nicotinic receptors. Among nicotine-naïve individuals, the $\alpha 4\beta 2$ nicotine receptor has high densities in thalamus, followed by midbrain, pons, cerebellum and cortex (Kimes et al., 2003). Comparisons of nonsmokers and recently abstinent smokers using SPECT (a method similar to PET) show that smokers have higher densities of $\alpha 4\beta 2$ nicotinic receptors both in cerebral cortex and in striatum (Staley et al., 2006). $\alpha 4\beta 2$ receptor upregulation in smokers was recently confirmed in a PET study (Mukhin et al., 2008). Finally, compared to nonsmokers, smokers have lower levels of brain monoamine oxidase (MAO), an enzyme that metabolizes brain amines including dopamine and serotonin (Fowler, Volkow, Wang, Pappas, Logan, MacGregor et al., 1996; Fowler, Volkow, Wang, Pappas, Logan, Shea et al., 1996). These lower levels of MAO are thought to be due to the ingestion of MAO-inhibiting compounds in cigarette smoke (Fowler, Logan, Wang, & Volkow, 2003) and may play a role—either independently or in synergy with nicotine—in smoking reinforcement.

Observed differences in brain structure and biochemistry between smokers and nonsmokers may reflect a number of factors, including the neuro-excitatory or -toxic effects of cigarette smoke constituents. In addition, smokers and nonsmokers may exhibit differences in brain structure and physiology that predate smoking, and which are related to psychological or cognitive risk factors for smoking (e.g. impulsivity). Additional studies that evaluate the effects of prolonged abstinence, and/or prospective studies that evaluate individuals prior to smoking, can help elucidate which factors are causes versus consequences of smoking.

The effects of smoking/nicotine

Nicotine is the key psychoactive agent in tobacco smoke and preclinical studies demonstrate that nicotine administration modulates the transmission of nearly all major neurotransmitter types (Levin, McClernon, & Rezvani, 2006). PET has been used to evaluate the effects of cigarette smoking on both dopamine release and nicotinic receptor binding in human smokers. With respect to dopamine, smoking a cigarette has been shown to stimulate dopamine release

in the ventral striatum (Brody et al., 2004)—a region which includes the nucleus accumbens and is critical to reward signaling. With respect to nicotine receptor binding, it has been demonstrated that smoking as few as 3 puffs of a cigarette results in occupation of the majority of brain $\alpha 4\beta 2$ nicotinic receptors, thus rendering them functionally inactive (Brody et al., 2006). Collectively, these studies suggest that smoking a cigarette significantly alters brain neurochemistry, but they leave open the question of the role of $\alpha 4\beta 2$ receptor subtype in smoking reinforcement beyond the first few puffs. Future studies that focus on other nicotinic receptor subtypes and neurotransmitter systems will help to further elucidate the effects of cigarette smoking on brain function.

The effects of smoking abstinence

Smoking abstinence results in significant withdrawal signs and symptoms, including craving and disruption of mood and cognition. Electroencephalography (EEG) studies demonstrate that smoking abstinence significantly alters brain physiology, as evidenced by increased power in low frequency bands (Gilbert et al., 2004; Gilbert et al., 1999). More recently, fMRI has been used to assess both the effects of smoking abstinence on basal brain physiology, and reactivity to smoking-related cues and cognition. Smoking abstinence reduces resting cerebral blood flow in anterior cingulate and orbitofrontal cortex, and the degree of reduction is related to background craving levels (Wang et al., 2007). Smoking abstinence also decreases transient responses to smoking-related cues in the ventral striatum (David et al., 2007) but increases sustained responses to these cues in dorsal striatum and prefrontal and parietal cortex (McClernon et al., under review). These findings suggest that smoking abstinence increases brain sensitivity to smoking-related cues in regions involved in reward, action initiation, and motivation. This may in turn account for the finding that exposure to such cues is an important precipitant of smoking lapse and relapse (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). Consistent with this finding, a preliminary study suggests that smoking cessation treatments designed to devalue smoking-related cues decrease brain cue-reactivity and that baseline cue-reactivity may be predictive of smoking cessation outcomes (McClernon et al., 2007).

In addition to effects on craving and cue-reactivity, smoking abstinence significantly disrupts a number of cognitive processes, including sustained attention and working memory (Gilbert et al., 2004; Mendrek et al., 2005). Coincident with decreases in performance, smoking abstinence increases left prefrontal activation during working memory (Xu et al., 2005), which suggests that abstinence decreases efficiency in this area. Consistent with this finding, studies of the effects of nicotine vs. placebo administration show that nicotine abstinence increases working memory related brain activation in regions subserving attention and memory, including the anterior cingulate cortex and dorsolateral prefrontal cortex (Ernst et al., 2001).

Neuroimaging of smoking/mental illness comorbidity

Only a handful of neuroimaging studies have focused on understanding the neural mechanisms underlying smoking and comorbid mental illness, and the majority of these studies have focused on comorbid schizophrenia. An MRI study compared smokers and nonsmokers with schizophrenia, and found that smokers with schizophrenia had greater grey matter volumes in prefrontal and temporal cortex (Tregellas et al., 2007). As noted by the investigators, this intriguing finding suggests that smoking may preserve grey matter among smokers with the disorder. However, as with similar studies in non-psychiatric samples (Brody et al., 2004; see above), these brain differences possibly predate smoking.

Functional neuroimaging studies of smoking-schizophrenia comorbidity have targeted cognitive processes shown to be 1) deficit in individuals with schizophrenia and 2) improved by nicotine administration (or conversely worsened by smoking/nicotine abstinence). An fMRI study of working memory (WM) in smokers with and without schizophrenia (Jacobsen et al.,

2004), found that among smokers without the disorder, nicotine led to increases in task-related activation in right occipital lobe (BA 19/37), and decreased activation in globus pallidus under the highest WM load. In contrast, among schizophrenic patients, nicotine increased activity in left insula, and right putamen and thalamus, again under the highest working memory load. These and other findings (Postma et al., 2006; Tanabe, Tregellas, Martin, & Freedman, 2006) suggest that smokers with and without schizophrenia may respond differentially to the effects of nicotine, and that these differences are mediated by specific brain systems.

A framework for neuroimaging of smoking-mental illness comorbidity

The brief review above highlights the power of neuroimaging techniques to elucidate neural mechanisms underlying nicotine dependence. Whereas a handful of studies have examined smoking-schizophrenia comorbidity, additional studies are needed to fully evaluate relations between smoking behavior and mental illness. Below, I provide a conceptual-methodological framework for applying neuroimaging techniques (see Table 1) to the study of dual diagnosis, using smoking-ADHD comorbidity as an example.

Individuals with ADHD smoke at disproportionately high rates (Molina & Pelham, 2003; Pomerleau, Downey, Stelson, & Pomerleau, 1995), report greater withdrawal symptoms (Pomerleau et al., 2003) and disruptions of cognition upon quitting (McClernon et al., 2008), and adult smokers with a history of childhood ADHD are more likely to relapse (Humfleet et al., 2005). Moreover, nicotine has been shown to improve attention in nonsmokers with and without ADHD (Levin et al., 1998; Potter & Newhouse, 2004). Modern neuroimaging techniques can be used to evaluate aspects of brain anatomy and function that will shed new light on the causes of this comorbidity.

Brain structure

Compared to adults without ADHD, individuals with the disorder have been shown to have decreased cortical thickness in regions including the right parietal cortex, dlPFC and ACC (Makris et al., 2007). These differences in grey matter, which are similar to the smoker-nonsmoker differences, may account for observed cognitive deficits inherent in ADHD. Thus, it is reasonable to hypothesize that smokers with ADHD might exhibit lesser frontal cortical grey matter volumes than smokers without this disorder. However, as with schizophrenia (see above), smokers with ADHD might have preserved or even increased grey matter compared to their nonsmoking counterparts. Future studies, particularly longitudinal ones, are needed to further evaluate the causes and consequences of smoking on brain structure among individuals with ADHD.

Neurochemistry

It has been hypothesized that the attentional and hyperactive/impulsive symptoms inherent in ADHD are due to dysregulated dopaminergic neurotransmission in striatal brain regions (Grace, 2001; Solanto, 1998). Given this and the known effects of nicotine on striatal dopamine, it has been hypothesized that smokers with ADHD may use nicotine to enhance dopamine neurotransmission, and consequently obtain improvements in ADHD symptoms (McClernon & Kollins, in press). Some evidence for neuronal adaptation following smoking in ADHD patients is seen in imaging studies, which have shown that smokers with ADHD have levels of dopamine transporter (DAT) that are similar to non-ADHD individuals, and to ADHD patients who have been treated with stimulant medication (Krause et al. 2000; Krause et al. 2002). Much additional work using PET and SPECT is needed to fully characterize smoking-ADHD interactions. Specific questions of interest include: Do ADHD and non-ADHD individuals differ in the density and distribution of nicotinic receptor subtypes? Are there

ADHD/non-ADHD differences in the degree to which nicotine stimulates striatal dopamine release?

Neurocognition

A number of investigators have posited that individuals with mental illness may smoke in order to enhance or restore some aspect of cognition (Sacco, Bannon, & George, 2004). As such, functional neuroimaging studies of smoking-mental illness comorbidity have targeted those cognitive processes that are 1) enhanced by nicotine administration or disrupted by smoking abstinence, and 2) deficient among individuals with a particular mental illness. Neuroimaging studies of smoking-schizophrenia, for instance, have examined the effects of nicotine and nicotine abstinence on working memory or sensory gating—both of which fulfill the above criteria. A similar approach could be taken by studying the effects of nicotine on response inhibition among smokers with and without ADHD. Individuals with ADHD are by definition more impulsive, and smoking abstinence has been shown to amplify behavioral measures of impulsivity in ADHD smokers (McClernon et al., 2008). Moreover, nicotine administration (Potter & Newhouse, 2004) and abstinence (Pettiford et al., 2007) result in increased and decreased behavioral inhibition, respectively.

Neurogenetics

Recently, combined analyses of genetic and neuroimaging data have been conducted. Such neurogenetic analyses provide insight into how genes are functionally related to behavior via neural processes. In the area of nicotine dependence, neurogenetic analyses have identified genotypic correlates of resting cerebral blood flow during smoking abstinence (Wang et al., 2008) and smoking cue reactivity (McClernon, Hutchison, Rose, & Kozink, 2007). Given the overlap in candidate genes that have been shown to be related to smoking and ADHD (McClernon & Kollins, 2008), it may be the case that particular genes interact with either ADHD or with cigarette smoking to influence ADHD or smoking related changes in brain structure and/or function. For instance, adult smokers carrying a specific gene variant might exhibit greater brain activation in response to nicotine administration, but only among ADHD individuals. Such gene $\times$ ADHD interactions might help explain how ADHD diagnosis leads to smoking in some but not all individuals with the disorder.

Pharmacological MRI (phMRI)

A number of studies have used fMRI to investigate the effects of drug administration on brain physiology. One such pharmacological MRI (phMRI) study demonstrated, for instance, that administration of nicotine resulted in increased BOLD signal in limbic (amygdala) and cortical (cingulate, PFC) brain regions (Stein et al., 1998). Much additional work is needed in this area to evaluate the effects of other pharmacological agents, including smoking pharmacotherapies (e.g. varenicline), on brain states and function. Studies that evaluate differences in brain drug responses in smokers with and without ADHD can potentially lead to a greater understanding of the mechanisms underlying this comorbidity and/or differential treatment response.

Summary

The review above suggests that modern neuroimaging techniques can provide new and unique insights into the neurobiological basis of nicotine dependence and its treatment. Whereas only a small number of studies have focused on smoking dual diagnosis, there are a large number of potential research questions that can be addressed across diverse patient populations using currently available technologies.

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Table 1

Neuroimaging domains, modalities and research questions applied to the study of ADHD-smoking comorbidity

Domain	Imaging Modality	Research Questions
Structure	MRI	<i>Do brain regions differ in size or shape between smokers with and without ADHD? Does the location/function of these regions suggest loci for smoking/ADHD pathophysiology?</i>
Neurochemistry	SPECT/PET	<i>Do nonsmokers with and without ADHD differ with respect to the distribution and/or density of nicotinic receptors? Does the magnitude of dopamine release following nicotine administration differ between ADHD and non-ADHD smokers?</i>
Neurocognition	fMRI/PET	<i>Does nicotine administration/abstinence differentially alter brain function during task performance in ADHD versus non-ADHD smokers?</i>
Neurogenetics	MRI/PET/fMRI	<i>Do specific genes moderate or mediate the relationship between smoking and ADHD effects on brain structure and function?</i>
Neuropharmacology	phMRI	<i>Does nicotine administration differentially change brain activation in ADHD and non-ADHD smokers? Does administration of other pharmacologic agents (e.g., dopamine promoters, nicotine replacement therapies) alter abstinence-induced brain states and function?</i>