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Neuroimaging, Genetics and the Treatment of Nicotine Addiction

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Abstract

Advances in neuroimaging and genomics provide an unprecedented opportunity to accelerate medication development for nicotine dependence and other addictions. Neuroimaging studies have begun to elucidate the functional neuroanatomy and neurochemistry underlying effects of nicotine and nicotine abstinence. In parallel, genetic studies, including both candidate gene and genome-wide association approaches, are identifying key neurobiological targets and pathways important in addiction to nicotine. To date, only a few neuroimaging studies have explored effects of nicotine or abstinence on brain activity as a function of genotype. Most analyses of genotype are retrospective, resulting in small sample sizes for testing effects of the minor alleles for candidate genes. The purpose of this review is to provide an outline of the work in neuroimaging, genetics, and nicotine dependence, and to explore the potential for increased integration of these approaches to improve nicotine dependence treatment.

Keywords

Neuroimaging; Genetics; Nicotine; Smoking; Pharmacogenetics; fMRI; PET

Introduction

Over 438,000 premature deaths each year in the U.S. are attributable to tobacco use [21]. Despite widespread awareness of these health risks, almost 21% of American adults are current cigarette smokers [22]. Nicotine, the addictive chemical in tobacco, produces a biological dependence, and therefore, even with the most efficacious medications available, only 1 in 4 smokers is able to maintain long-term abstinence [128]. With the extensive morbidity and mortality associated with this chronic relapsing disorder, there is an urgent need to develop better therapies to aid in smoking cessation. Emerging technologies, such as genomics and

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neuroimaging, can facilitate drug discovery and development, as well as individualized therapy for nicotine dependence [9,81,85].

Neuroimaging approaches offer a powerful tool to elucidate the functional neuroanatomy and neurobiological processes underlying nicotine dependence [10,99]. Magnetic resonance imaging (MRI) can relate nicotine dependence to examine individual differences in brain morphology, and functional MRI (fMRI) can measure changes in regional brain activation associated with different nicotine dependence states (e.g., abstinence vs. satiety). Blood oxygen level dependent (BOLD) fMRI is widely used to examine the pattern of neural activity in response to neurobehavioral probes (i.e., cognitive tasks). This approach capitalizes on the paramagnetic properties of deoxyhemoglobin and a contrast is generated from the vascular coupling of blood flow to neuronal metabolism [114]. Increased oxyhemoglobin occurs in activated brain regions. In the context of nicotine dependence, BOLD fMRI has been used to identify the functional neuroanatomy underlying cigarette cravings or cognitive performance following nicotine delivery or abstinence. Arterial spin labeled (ASL) MRI quantifies individual differences in regional CBF in absolute physiological units (ml/100g/min) by magnetically labeling water molecules in the arterial blood as an endogenous tracer that has sufficient decay time to visualize dynamic changes in brain perfusion [34]. This approach may be optimal for exploring effects of smoking or abstinence in a resting state [156,157], but can also be used to study cue probe effects [42].

Positron emission tomography (PET) utilizes radioactive compounds such as labeled water or glucose that can measure CBF or cerebral glucose metabolism, or radio-labeled ligands that bind to specific receptors and can estimate receptor function and neurotransmitter availability in the brain [119,154]. Unlike fMRI, PET imaging can clarify neurochemical processes, as the radioligands have binding specificity to particular neuronal receptor subtypes [15,129]. Another imaging technique that utilizes radio-labeled compounds is single photon emission computerized tomography (SPECT) [73,94].

These neuroimaging approaches provide complementary information to elucidate where and how nicotine (and abstinence from nicotine) produces effects in the brain that may maintain nicotine dependence. While fMRI can more precisely localize regions that are differentially activated in specific states or among individuals, PET and SPECT can identify particular receptors or neurochemical pathways underlying different activation patterns. These approaches can clarify the pathobiological processes that contribute to nicotine dependence, elucidate the neural substrates of behavioral effects of nicotine dependence, and suggest mechanisms through which efficacious smoking cessation medications can reverse these behavior and brain processes. This information can, in turn, facilitate target identification for medication discovery, as well as the selection of promising compounds based on their neural signatures.

Emerging genomic technologies are advancing our understanding of inherited biological influences on nicotine dependence [85,86]. This line of research promises to clarify the contribution of genetic factors to the substantial variability in medication response rates in smoking cessation trials and identify those smokers most likely to experience adverse events. By incorporating genetic approaches into neuroimaging research, progress in medication development may be greatly accelerated.

The goals of this paper are (1) to summarize what is known about the neural substrates of nicotine dependence, including evidence from neuroimaging investigations of nicotine's pharmacologic effects, conditioned responses (ie, smoking cues), and nicotine abstinence effects; (2) describe emerging research on the genetic basis of different smoking behavior phenotypes, including the development of nicotine dependence, smoking cessation, and

response to different therapies; (3) review existing studies that integrate neuroimaging and genetics to study response to medications; and (4) provide a brief outline of potential future research directions in this area. We begin with a brief overview of the neurobiology of nicotine dependence, as this foundation is essential to generate hypotheses for neuroimaging and genetic studies.

Neurobiology of Nicotine Dependence

Nicotine binds to the neuronal nicotinic acetylcholine receptors (nAChRs) located on the dopaminergic cell bodies [107] in the ventral tegmental area (VTA). The predominant nAChRs in the VTA are of the $\alpha 4\beta 2$ subtype which has greater affinity for nicotine as compared to homomeric nAChRs comprised of $\alpha 7$ subunits [161] that are in lower abundance in the VTA [23,69]. Stimulation of these nAChRs by nicotine produces a shift from tonic firing of dopaminergic neurons to burst firing, resulting in increases in DA levels in the nucleus accumbens (NAC) and rewarding effects [47,95,112].

The VTA dopaminergic pathway is also under the influence of other neurochemical modulators as the GABA-ergic interneurons [66] and the GABA-ergic innervations from the NAC [155]. These neurons provide inhibitory control over dopaminergic neurons, whereas glutamergic efferents from the prefrontal cortex (PFC) [130] and cholinergic inputs from the tegmental pedunclopontine nucleus (TPP) [25] have stimulatory effects on the VTA. The GABA-ergic neurons have predominantly the $\alpha 4\beta 2$ nAChR subtype [69] that desensitize quickly, whereas the pre-synaptic nAChRs on the glutamergic terminals are mainly of the $\alpha 7$ subtype [65] which are slower to desensitize [96]. Thus with nicotine exposure, inhibitory control (GABA) is reduced and the positive glutamergic control increases, contributing to long-term plasticity of behavior. The cholinergic projections from TPP also influence the firing of the VTA dopaminergic neurons via the muscarinic nicotinic receptors [166,167].

Lastly, there is evidence of involvement of the endogenous opioid pathway in nicotine dependence. Nicotine administration causes release of endogenous opioid peptides such as β -endorphin that binds to mu opioid receptors (MOR) which are located on the GABA-ergic interneurons in the VTA [28]. This stimulation of the MORs produces disinhibition of the GABA-ergic interneurons and increases DA release in the NAC [1]. Chronic nicotine administration also causes upregulation of MORs in the striatum [160].

Neuroimaging Research on Nicotine Dependence

Nicotine delivery in smokers and non-smokers

To study the effects of nicotine delivery on brain function, various routes of administration have been used, including: intravenous (i.v.) delivery, nicotine nasal spray, and nicotine gum. Investigation of nicotine effects in non-smokers provides an opportunity to examine the neuropharmacological effects nicotine, without confounding by the effects by either smoking history or conditioned brain responses in chronic smokers.

Nicotine delivery induced brain metabolism and activation changes—In a PET study, i.v. nicotine (1.5mg) administration to healthy *non-smoking* adults reduced cerebral metabolism by 5–16% in most regions of the brain (i.e., superior frontal gyrus, inferior frontal gyrus, anterior cingulate gyrus, insula, parahippocampal gyrus, cuneate sulcus, caudate nucleus, putamen, and cerebellar cortex), except the medial thalamus [138]. However, in a study of *smokers*, i.v. nicotine, compared to placebo, produced dose-related increases in activation in insula, anterior and posterior cingulate cortex, frontal lobes, temporal and visual cortex, NAC, amygdala, hypothalamus and limbic thalamus [139]. Thus, the effects of i.v. nicotine on human brain activation differ depending on smoking history.

Effects of nicotine delivery on the task invoked brain activation changes—

Kumari and colleagues compared effects of i.v. nicotine (12µg/kg) to saline injection in nonsmokers who performed a working memory task. Nicotine, relative to placebo, increased activation in the right anterior cingulate cortex, superior frontal cortex, and superior parietal cortex during performance of a working memory task, with variations in activation and performance at different working memory loads [72]. In contrast, during a smooth pursuit eye movement task, nicotine gum administered to non-smokers reduced hippocampal and amygdala activation [145]. Among smokers, however, increases in right hemisphere activation (Rt. PFC, anterior cingulate, and right inferior parietal cortex) were observed during performance of a working memory task (following placebo gum administration), and this effect was reduced with nicotine gum [37]. In-contrast, ex-smokers had greater left hemisphere activation during task performance suggesting that different cognitive strategies being were being used by current and former smokers [37]. In another study, a 21mg transdermal nicotine patch increased BOLD signal in the bilateral occipital cortex, left thalamus, bilateral caudate nuclei while smokers completed a rapid visual information processing (RVIP) task [76]. Thus, studies of nicotine delivery during task performance also demonstrate differences in brain activation based on subject's smoking status. Effects amongst smokers also vary based on the mode of nicotine delivery, and perhaps the specific cognitive task employed.

Neurochemical effects—Brody and colleagues examined the effects of smoking on 2-FA binding, a highly specific ligand developed for visualization of $\alpha 4\beta 2$ nicotinic receptors. They determined that the effective dose that would occupy approximately 50% of the nAChRs in the thalamus, brainstem and cerebellum was 0.19 ± 0.05 of a cigarette [13]. The fractional occupancies assessed at 3 hours after 1 puff, 3 puffs, 1 full cig or smoking to satiety were 33%, 75% 88%, and 95% respectively [13]. This study provides evidence that it takes a small amount of smoking to desensitize the $\alpha 4\beta 2$ receptors and that these receptors remain saturated throughout the day.

PET studies with the specific radio-labeled ligand for the dopamine D2 receptor (^{11}C) raclopride have documented nicotine effects on dopamine release. Nicotine nasal spray produced reductions in binding of the raclopride ligand (note: reduced ligand binding reflects increased release and binding of dopamine) and these effects correlated with improved mood [108]. Nicotine gum also decreased (^{11}C)raclopride binding in the ventral striatum amongst smokers, with no effect on non-smokers [143]. Reductions in (^{11}C)raclopride binding potential have also been demonstrated in the left ventral basal ganglia, with a binding difference of 10% between smoking a nicotine (greater dopamine release) vs. a de-nicotinized cigarette [129]. These studies using multiple modes of nicotine delivery, all provide evidence that nicotine increases dopamine release.

Nicotine Abstinence Effects

Several studies have explored the neural pathways or regions that are sensitive to abstinence from nicotine in chronic smokers.

Resting CBF and metabolism (abstinence vs. smoking)—To explore effects of nicotine abstinence on regional CBF (rCBF), a recent study compared resting rCBF after overnight (>12hrs) abstinence and during smoking as usual, using ASL perfusion MRI [156]. Abstinence (vs. satiety) was associated with rCBF increases in the medial orbitofrontal cortex (OFC) and left OFC, and decreases in right prefrontal cortex (PFC) [156]. This study also explored the neural substrates of abstinence-induced smoking urges, using a measure of urge to smoke shown previously to predict clinical relapse [68]. Increases in smoking urges (abstinence vs. satiety) were associated with increased rCBF (abstinence vs. satiety) in several regions in the brain's reward and visuo-spatial circuitry (right DLPFC, OFC, left inferior frontal

cortex, occipital cortex, ACC, ventral striatum/nucleus accumbens, thalamus, amygdala, bilateral hippocampus, left caudate, right insula, and medial temporal gyrus) [156]. Also abstinence-induced increases in withdrawal scores were associated with increases in rCBF in the right DLPFC, caudate and right hippocampus [156].

Overnight abstinence after 2 weeks of smoking de-nicotinized cigarettes while using a transdermal nicotine patch demonstrated a decrease in regional blood flow assessed by radiolabeled water in the right anterior cingulate as compared to overnight abstinence at baseline or after 2 weeks of smoking regular brand cigarettes [123]. Metabolic activity in the thalamus was positively correlated with nicotine dependence, metabolic activity in the ventral striatum was negatively correlated with withdrawal symptoms, and metabolic activity in the OFC was also negatively correlated with cravings [123]. Tanabe and colleagues scanned 12 healthy smokers while they were smoking as usual. after 16–18hrs of overnight biochemically verified abstinence, and after chewing a 6mg nicotine gum during the abstinent session [144]. There was a significant inverse correlation between withdrawal symptom score and thalamic CBF, while nicotine replacement reversed the CBF effects and withdrawal symptoms [144].

In a PET study, smoking the first cigarette of the day following overnight abstinence was associated with increases in CBF in the cerebellum and right occipital cortex compared to the 1st scan after overnight abstinence; and decreases in CBF were observed in the nucleus accumbens (NAC), bilateral occipital cortex, ventral AC, right parietal cortex, right fusiform and the right hippocampus [171]. Decrease in craving scores from overnight abstinence to smoking the 1st cigarette correlated with decreases in CBF in the dorsal anterior cingulate, and the right hippocampus [171]. In a previous study using the same imaging paradigm administration of nicotine nasal spray decreased CBF in the left temporal cortex, right amygdala and increased CBF in the right thalamus after overnight abstinence [170]. The studies described in this section used different methodologies to assess effects of abstinence and nicotine re-exposure on regional brain activation. Thus, it is difficult to draw conclusions and to ascertain the direction of association of withdrawal symptoms and craving with activation values across studies and regions of interest.

Change in brain activation with task probes—Several studies in the literature have demonstrated that abstinence from nicotine is associated with deficits in attention and working memory [60,164]. A handful of neuroimaging studies have helped delineate underlying structures and pathways potentially mediating this decrement in performance. For example, in adolescent smokers, 24 hours of abstinence produced worse performance on the 2-back condition of the n-back working memory task that was accompanied by increased activation in right inferior gyrus, right medial/superior frontal gyrus, right superior frontal gyrus, left insula, right fusiform gyrus, right superior/inferior parietal lobe, right caudate [60]. The effect of a prenatal history of exposure to nicotine modulated this increase in activation during a visuo-spatial and encoding task [62]. Xu and colleagues examined smokers while performing the letter n-back task working memory task after overnight abstinence. At a lower memory load (1-back condition), DLPFC activation was increased in abstinence relative to smoking; while there were no differences at higher working memory load [164]. The same group extended these findings by allowing participants to smoke halfway through the session and then repeat the n-back task. They observed that task-related BOLD signal increased from the 1- to the 3-back condition if participants were abstinent prior to the cigarette; however the BOLD signal decreased from the 1- to the 3-back condition if participants were allowed to smoke as usual at the start of the session [165].

Neurochemical effects—Two recent SPECT imaging studies utilizing specific ligands to the nicotinic receptors (nAChRs) scanned smokers after differing intervals of nicotine abstinence. In one study, an increase in $\beta 2$ nAChRs by about 25–35% (as compared to non-

smokers) was observed after short-term abstinence in the cortical areas, striatum and cerebellum [136]. A negative correlation was also observed between binding to $\beta 2$ -containing nAChRs and the urge to smoke to relieve withdrawal symptoms. These findings were confirmed in a subsequent SPECT study that also observed an increase in $\beta 2$ -containing nAChR binding initially (first 4 hours), with a return to baseline binding levels after 21 days of abstinence [94]. These data suggest that $\beta 2$ -containing nAChRs may play a critical role in abstinence-induced cravings.

Smoking Related Cues

The brain circuitry that underlies cue-elicited cravings to smoke has been explored extensively among smokers using positron emission tomography (PET) and functional MRI (fMRI) [10]. Compared to neutral cues, presentation of smoking-related cues either as pictures, smoking videos or even 3-D environment simulation have been associated with increased activation in the visuo-spatial, attention, and reward circuitry [12,30,35,78,98,100]. However, these studies varied with respect to the abstinence status of smokers, and only two studies compared cue-induced craving between abstinent and non-abstinent states [100]. Expectancy to smoke measured post-scan correlated with increased cue-induced activation [98]. The key regions that were activated included ventral striatum, orbitofrontal cortex, anterior cingulate, fusiform gyrus, temporal lobe, prefrontal regions, posterior amygdale, posterior hippocampus, medial thalamus, caudate nucleus. Another recent study controlled for the effects of nicotine withdrawal and demonstrated that smoking cues activated these regions even when smokers were allowed to smoke ad-lib prior to brain imaging [42]. Some brain regions, such as the anterior cingulate cortex, right orbitofrontal cortex, left inferior occipital gyrus, left globus pallidus, right caudate, left inferior parietal lobe, and medial occipital lobes have shown cue-induced BOLD activation that is positively correlated with levels of nicotine dependence [102,134]. Similarly brain activation in mesocorticolimbic region, midbrain and amygdala have been positively correlated with cue-induced craving scores [134]. Lastly gender and race have been shown to have a moderating effect on cue-elicited brain activation [102,115]. Thus, studies of cue-induced craving provide consistent evidence of increased activation in the regions involved in nicotine reward and visual attention independent of abstinent status.

Summary and Interpretation of Nicotine Dependence and Neuroimaging Research

Nicotine delivery—In smokers, nicotine delivery activates frontal cortical regions that are important for executive cognitive function and behavioral control, regions involved in monitoring reward and stimulation such as the ACC, regions associated with the experience of reward such as the nucleus accumbens and ventral striatum, as well as regions involved in monitoring internal physiological states like the insula [138,139]. Some studies indicate that increased activation in these regions may also facilitate performance on neurocognitive tasks following nicotine delivery [37,72]. PET studies show that nicotine administration desensitizes $\alpha 4\beta 2$ -containing nAChRs [13], and as receptor occupancy decreases over time, smoking urges increase [136]. Nicotine also causes dopamine release in the ventral striatum [108,143].

Nicotine abstinence—Nicotine abstinence increases activation in brain areas associated with the visuo-spatial and reward circuitry [156]. Importantly, abstinence-induced craving and withdrawal are associated with altered CBF; however the direction of effects is not consistent across studies [123,144,156,170]. While performing cognitive tasks during abstinence, smokers exhibit decreased performance and greater activation in the areas associated with executive cognitive functioning such as dorsolateral PFC [60,164]. Short term nicotine abstinence has been shown to increase levels of unbound $\beta 2$ nAChRs that appear to normalize after a few weeks [94,136]. These studies provide several clues as to why the first few days of abstinence is a critical period for relapse.

Smoking Cues—Cigarette or smoking related cues, independent of the smoker's abstinent state have been consistently shown to cause greater activation in the brain's visuospatial, attention and reward circuitry [42,100].

Brief Overview of the Genetic Basis of Nicotine Dependence

The heritability of nicotine dependence and smoking persistence has been documented extensively in twin studies. For example, about 60–70% of the variance in nicotine dependence, and about 50% of the variance in quitting success is attributable to inherited factors at about 60–70% [86,140,163]. This work has been extended and there is a large body of research on specific genetic associations with various smoking behavior phenotypes. Amongst the genes examined for associations with smoking behavior, the role of the cytochrome P450 *CYP2A6* gene has been most widely replicated [93,109]. Faster metabolizers of nicotine (those with the *CYP2A6* wildtype genotype) smoke more cigarettes per day [92], have higher levels of nicotine dependence [71,92] and are more likely to relapse back to smoking following a quit attempt [48].

Considering pharmacodynamic targets, genes coding for nAChR subunits are obvious candidates for association with nicotine dependence. Published studies have suggested associations of nicotine dependence with variants in *CHRNA4* (encoding $\alpha 4$ receptor subunit) [40,58,87], *CHRNA1* (encoding $\beta 1$ subunit) [89], and *CHRNA5* and *CHRNA3* (encoding the $\alpha 3$ and $\alpha 5$ subunits) genes with ND [2,46,125,146]. Two studies examining variants in *CHRNA2* (encoding the $\beta 2$ subunit) were negative [90,133], however these studies have examined variants of unknown function and coverage across the genes was limited.

Based on knowledge of the neurobiology of nicotine addiction, genes associated with the dopamine pathway have been investigated. Earlier studies focused on a common Taq 1A variant in the *ANKK1* gene (about 10kb upstream of *DRD2* [111] and associations with smoking status were found [27,56,135]; however these associations were not uniformly replicated [8, 149]. Likewise, some studies have identified differences between smokers and non-smokers in the prevalence of a common variant in the dopamine transporter (*SLC6A3*) gene [79,124, 137,147]; however other studies reported negative findings [152]. Additional associations with smoking behavior reported in the literature include the dopamine D4 receptor (*DRD4*) [132, 153]; dopamine D3 receptor (*DRD3*) [57]; catechol-o-methyl transferase (*COMT*) (a dopamine metabolizing enzyme) [6,26,148]; dopamine beta-hydroxylase (DBH) (a dopamine metabolizing enzyme) [43,104]; DOPA decarboxylase (involved in synthesis of dopamine, serotonin, and norepinephrine) [91,168]. While genes in other pathways have been studied less extensively; there is evidence relating smoking behavior and nicotine dependence with functional variants in the mu opioid receptor (*OPRM1*) [84,121,169] and brain derived neurotrophic factor (*BDNF*) [5,74] respectively. Additional genes associated with nicotine dependence such as neurexin-1 (plays a role in synaptogenesis) [7,113]; beta arrestin (proteins that are involved in regulation and trafficking of dopamine and opioid receptors) [141]; and neurotrophic tyrosine kinase receptor 2 gene (*NTRK2*) (transducer signals for neuronal survival) [4] have also been described.

High throughput genotyping of single nucleotide polymorphisms currently allows parallel assessment of up to 1 million individual polymorphisms in a single experiment. By carefully choosing SNPs corresponding to empirically determined blocks in linkage disequilibrium (the HapMap project), these newer genotyping technologies enable comprehensive coverage of the human genome. One strength of this whole genome association study (WGAS) approach is that it is essentially hypothesis free and enables association of both known protein encoding gene loci as well as non-protein encoding loci, thereby identifying novel genes and SNPs. Such studies have implicated metabotropic glutamate receptor 6, RAR-related orphan receptor B,

and catenin alpha 3 [2,7,88,125]. Also, recent genome wide association studies of smoking cessation identified several novel genes involved in cell adhesion and signaling [150,151]. The role of the *CHRNA3-CHRNA5* gene cluster in nicotine dependence is becoming increasingly important as this cluster was associated with nicotine dependence in whole genome association study [125], and has also been recently replicated in another study [146].

An increasing number of studies are applying these genetic approaches to identify smokers most and least likely to benefit from specific pharmacotherapies for nicotine dependence, with the goal of optimizing treatment outcomes through the use of individualized treatment strategies. Currently approved therapies for nicotine dependence include nicotine replacement therapies (nicotine patch, gum, spray, inhaler, lozenge) bupropion (an anti-depressant that inhibits dopamine uptake), and varenicline (an $\alpha 4\beta 2$ nAChR partial agonist) [128].

Polymorphisms in *CYP2A6*, a nicotine metabolizing enzyme, have been associated with smoking behavior, medication usage, and treatment levels of nicotine among smokers treated with nicotine replacement therapy [92]. *CYP2A6* genotype also correlates significantly with the ratio of nicotine metabolites, 3-hydroxycotinine (3-HC)/ cotinine, suggesting the utility of measuring markers of nicotine metabolism in pharmacogenetic studies [92]. Among smokers treated with the nicotine patch, there was a 30% decrease in the odds of successful quitting with each increasing quartile of the nicotine metabolite ratio [83]. While faster metabolizers of nicotine perform more poorly with a standard dose of nicotine patch, bupropion is highly efficacious for this group [116]. The *CYP2B6* enzyme is expressed in the brain, and individuals with low activity allele for the *CYP2B6* enzyme also had a higher liability to relapse when on placebo, and this effect is offset by bupropion treatment [77]. Additionally, an interaction was observed between the *CYP2B6* and the *ANKK1* Taq1A polymorphism, as these individuals with the low activity allele at *CYP2B6* and with the A2/A2 genotype for the *ANKK1* Taq1A polymorphism had a higher likelihood of being abstinent at the end of treatment [29].

Of the nAChRs subunit genes mentioned above, the TC genotype at 3' UTR SNP rs2236196 on the *CHRNA4* gene has been associated with quitting success with nicotine nasal spray [58], while an intronic SNP of unknown function on the *CHRNA5* gene has been associated with response to bupropion in a Bayesian analysis [53]. The *DRD2* - 141Ins/DelC promoter polymorphism (that affects transcription) and *DRD2* C957T (that affects mRNA stability) have been associated with the efficacy of NRT and bupropion [80]. The *DRD2* Taq1A polymorphism (located on *ANKK1*) and a common *DRD4* polymorphism has also been associated with treatment response to NRT [31,64] and bupropion [32]. The val or high activity allele of the *COMT* val¹⁵⁸met polymorphism (associated with lower brain levels of dopamine) has been associated with quitting success on NRT [26,63,110] and a particular haplotype on the *COMT* gene (that included the val/met polymorphism) has been associated with treatment success on bupropion [3]. Gene by gene interactions involving the *DRD2/ANKK1* Taq1A polymorphism and the *SLC6A3* variable tandem repeat polymorphism [82,142] as well as *DBH* repeat polymorphism [64] also have been shown to predict abstinence.

Among the pharmacogenetic studies of nicotine dependence treatment, the most consistent associations have been observed for functional polymorphisms in nicotine metabolizing enzymes (*CYP2A6* and *CYP2B6*) and *COMT*. Associations of other dopaminergic are suggestive, but require independent replication. Although associations of the nAChR $\alpha 3/\alpha 5$ gene cluster with nicotine dependence have been replicated, these SNPs have yet to be associated with prospective smoking cessation or treatment response

Combining Genetics and Imaging in Nicotine Dependence

To date, only 4 published studies have explored the neural substrates of nicotine dependence using neuroimaging and genetics. One PET study examined associations of dopaminergic gene

variants with smoking-induced DA release using the radio-tracer [^{11}C]raclopride [14]. Smokers carrying variants associated with reduced dopaminergic tone (i.e., individuals with the 9-repeat allele for a VNTR in the dopamine transporter gene (*SLC6A3*), the short allele of the dopamine D4 receptor gene (*DRD4*) VNTR, or the (*COMT*) val/val genotypes) had greater smoking induced decreases in raclopride binding in the striatum, indicative of greater DA release in this region. There was no effect of the (*ANKK1*) Taq1A polymorphism on binding potential. Greater smoking-induced DA release was also associated a greater reduction in craving scores in those individuals [14].

Jacobsen and colleagues examined the association of the dopamine D2 receptor gene (*DRD2*) C957T polymorphism with brain activation during a working memory task (n-back) following pre-treatment with nicotine vs. placebo patch. Carriers of the 957T allele showed greater activation on nicotine patch during the 2-back task in the left anterior insula, left cerebellum, right and middle occipital gyri, right fusiform, and the right middle temporal gyrus. Conversely, individuals with the 957 C/C genotype at this locus showed decreased activation in these areas when they were on nicotine patch [61]. Individuals with 957T allele also had worse performance when they were on nicotine patch. The authors hypothesize that nicotine might have produced greater than optimal levels of dopamine in participants with the */T allele, resulting in poorer performance [61].

McClernon and colleagues demonstrated an association between the *DRD4* VNTR and smoking cue-reactivity. Individuals with the longer-repeat alleles had greater BOLD signal to the smoking cues in the right superior frontal gyrus and the right insula [101]. This finding is also consistent with behavioral studies that previously demonstrated that smokers with the *DRD4* long-repeat alleles have greater cue-provoked cravings [59], and are more likely to relapse following smoking treatment [31,132].

Lastly, associations between rCBF changes after overnight abstinence and functional polymorphisms in the dopaminergic and opioidergic pathways were examined recently [157]. Significantly greater abstinence-induced rCBF increases were found in regions previously linked with cigarette cravings among carriers of the DelC variant of *DRD2*-141 and among the *COMT* val/val group [157]. Smokers with TT genotypes for the *DRD2* C957T exhibited less change in rCBF in abstinence relative to satiety, compared to those with CC or CT genotypes [157]. Finally, smokers with *OPRM1* AA genotypes showed significant increases in CBF in regions associated previously with cigarette cravings [157]. These data suggest that some genetic variants associated with reduced dopaminergic tone, and those associated with increased endogenous opioid binding, may be linked with patterns of regional brain activation that may increase risk for relapse.

While few studies in the nicotine dependence field have integrated neuroimaging and genetics, the potential utility of this approach is well established in studies examining intermediate phenotypes relevant to nicotine dependence. Many of these studies have examined the variable tandem repeat polymorphism (*5-HTTLPR*) in the serotonin transporter gene, which affects expression levels of the transporter (short allele has reduced transcription) [51]. The 'short' allele has been associated with anxiety traits [159] and thus task probes that evoke an emotional response and activate the amygdala have been utilized to explore effects of the *5-HTTLPR* polymorphism. Using a perceptual processing task Hariri and colleagues observed that 20% of the variance in amygdala activation could be accounted for by the *5-HTTLPR* polymorphism with greater activation observed amongst participants with the 'short' allele [50]. Greater amygdala reactivity amongst the 'short' allele carriers has been replicated by several groups [17,20,45,49,52]. An explanation of the above mentioned effect could be that the 'short' allele carriers also have lower coupling and functional connectivity between the perigenual cingulate and the amygdala, and tight coupling between these regions serve as a feedback loop involved

in the extinction of negative affect [118]. Also healthy (non-psychiatric) individuals with the S/S genotype at the 5-HTTLPR polymorphism had lower resting rCBF as compared to the L/L genotype group in the amygdala and ventromedial prefrontal cortex [120]. A common polymorphism in the tryptophan hydroxylase gene also has been shown to affect amygdala reactivity in response to face- processing tasks [18,19].

Another genetic polymorphism that is well studied in the imaging field is the *COMT* val¹⁵⁸met polymorphism, which has also been associated with smoking behavior (see above). The high activity val allele is associated with decreased dopamine levels in the pre-frontal cortex [105], and inefficient processing indicated by greater activation (using BOLD fMRI or PET) in the DLPFC at the same level of performance [36,55,105,162]. Among healthy adults, val allele carriers have greater variability in their BOLD signal during cognitive task performance as well as increased baseline noise [162]. Another study found a dose-response effect of val alleles on PFC activation levels during performance on a 'n-back' task [36]. This BOLD activation was differentially affected in response to amphetamine while performing the 'n-back' task. Individuals with the met/met genotype had better frontal function during higher memory load (3-back condition) that worsened on amphetamine administration [97]. A saccadic eye movement task with healthy adults has demonstrated that val allele carriers have lesser BOLD response in the ventromedial and dorsomedial PFC during antisaccades (measures ability to suppress a unwanted reflexive response) and greater BOLD response in the posterior cingulate and precuneus during prosaccades (measures shift of attention) [39].

With respect to other genes and phenotypes, functional genetic variants in the dopaminergic pathway (*SLC6A3* VNTR, *DRD2* -141 Ins/Del C, and *DRD4* VNTR) predicted around 9–12% of the individual variability in ventral striatal reactivity in response to positive and negative feedback-associated monetary reward [41]. Specifically, there was greater ventral striatal reactivity observed with the *SLC6A3* 9/* allele, *DRD2* -141 DelC/* and *DRD4* 7-repeat carriers (all of these genotype groups should be associated with increased striatal dopamine release and decreased post-synaptic inhibition) [41].

Application of Neuroimaging Research to Understand Treatment Response

Neuroimaging technologies represent an excellent paradigm for elucidating the pathways and functional neuroanatomy underlying medication effects, providing a “neural fingerprint” of efficacious medications or treatment response against which promising novel compounds can be compared and selected [9].

Only one study, to date, has applied neuroimaging to elucidate the brain substrates of response to pharmacotherapy for nicotine dependence. This pilot study demonstrated that bupropion compared to placebo attenuated cigarette-cue induced activation in the anterior cingulate using FDG-PET [11]. Bupropion also however increased metabolic activation in the left lateral posterior temporal lobe in these smokers on exposure to the cues [11]. Additional studies of treatment for other addictions may also be informative.

In one study of alcohol-dependent individuals, treatment with the atypical dopamine D2/D3 antagonist amisulpride was associated with significantly lower BOLD activation elicited by alcohol-cues in the right thalamus, compared to pretreatment scan [54]. Kosten and colleagues found that increased pretreatment BOLD signal to cocaine cues in the left precentral and right superior temporal cortices was positively correlated with treatment effectiveness [70]. Additionally, a contrast between relapsers and nonrelapsers in the study revealed activation differences in the right precentral cortex and right posterior cingulate [70]. In a PET study, methadone-maintained individuals had greatest activation in the left orbitofrontal cortex compared to healthy controls, and the degree of activation on the left OFC correlated significantly with the number of years of abuse in the (untreated) heroin abusers group [38].

Since there is paucity of literature on neuroimaging and response to addiction treatment, we shall further illustrate the potential of this approach based on data from other psychiatry disorders. With respect to brain morphology in patients with major depression, symptom improvement after fluoxetine treatment was greatest amongst patients with greater gray matter volume in the cingulate cortex, left PFC and OFC, caudate nucleus, right inferior parietal, temporal and occipital cortices, insula, brainstem and cerebellum [24]. This variation in grey matter volume explained approximately 64% of the variance in symptom improvement [24]. Also, compared to non-responders, responders to venlafaxine therapy for major depression exhibited increased metabolism in the posterior cingulate between a post-treatment (8 weeks) to pre-treatment scan; and decreased metabolism in the left inferior temporal cortex, right nucleus accumbens, and posterior sub-genual cingulate between the post-treatment to pre-treatment scan [67]. Also, higher levels of pre-treatment metabolism in the left OFC was associated with worse outcome on paroxetine therapy [16], while lower metabolism in the bilateral OFC [127] and striatum [126] were associated with symptom improvement in obsessive compulsive disorder.

Other studies illustrate the value of utilizing neurobehavioral task probes to understand the neural basis of response to pharmacotherapy. For example, two studies used a facial emotion identification task probe to compare responders and nonresponders to fluoxetine. Greater functional brain activation in the anterior cingulate cortex was associated with greater treatment response to 8-weeks of fluoxetine therapy [24,44]. Lorazepam compared to placebo, was effective in reducing bilateral amygdala and insula activation while healthy volunteers performed an emotional faces task that helps delineate neural circuits affected by anxiolytic medications [117]. Likewise, left amygdala activation during this task predicted therapeutic response to anti-depressants for generalized anxiety disorder [103]. In a test of response inhibition (the Go/No-Go task), greater BOLD activation during successful inhibitions in the left amygdala, insula and nucleus accumbens predicted better treatment response to s-citalopram for major depression [75]. Activation in the rostral anterior cingulate during commission errors (unsuccessful stopping) on the task was also associated with greater post-treatment improvement in depression symptoms [75].

Conclusions and Future Directions

The integration of neuroimaging, genetics, and pharmacotherapy research could accelerate medication development for nicotine dependence in several ways. First, these studies could improve our understanding of the neurobiology of nicotine dependence by elucidating the brain mechanisms underlying associations of genetic polymorphisms and specific nicotine dependence phenotypes. These phenotypes may include, but are not limited to, nicotine's rewarding effects, nicotine abstinence symptoms such as urges, cognitive performance, and affect regulation, and smoking cessation. Second, the identification of responders and non-responders to treatment, using a combination of both genetics and neuroimaging, may provide a more powerful pre-treatment risk assessment than either tool alone. Lastly, pharmacological neuroimaging can be used to characterize the profiles of medications known to be effective for nicotine dependence treatment, against which novel compounds can be compared and selected. Adding a genetics component to these studies may allow for detection of a stronger signal for medication effects in subgroups of smokers. Examples of such approaches are highlighted in the following paragraphs.

To further our understanding of the neurobiology of nicotine dependence, variants in the nAChR subunit genes that have been associated with a smoking phenotype can be explored in neuroimaging studies. For example, smokers could be selected prospectively based on genotype and then genotype groups can be compared with respect to nAChR binding (in PET or SPECT studies) or rCBF alterations following nicotine delivery or nicotine abstinence. The

neurochemical substrates of the functional *DRD2* SNPs can also be examined using PET imaging, building upon the work of Brody and colleagues [14]. Further, fMRI studies incorporating neurobehavioral probes for affective or cognitive function can elucidate the specific mechanisms contributing to relapse in smokers with genetic susceptibility.

Neuroimaging can also be used to delineate the neural substrates of medication effects. Within-subject cross-over designs may be preferable for these studies, as each subject serves as their own control, thereby increasing statistical power and cost-efficiency. Candidate genes should be selected for such studies based on a medication's pharmacokinetics and pharmacodynamic effects. For example, bupropion effects on rCBF or receptor binding can be compared between groups of smokers with different genotypes for dopaminergic or nAChR genes or for the bupropion metabolizing enzyme CYP2B6. Likewise, effects of the new partial $\alpha 4\beta 2$ nAChR partial agonist varenicline could also be compared with fMRI or PET within smokers characterized genetically for SNPs in *CHRNA4* and *CHRNA2* (nAChR subunit genes). Associations of key variants in *CHRNA3/CHRNA5* with neural responses to nicotine or abstinence using fMRI or PET would also be informative, based on prior genetics and nicotine dependence work [125].

Neuroimaging could also help us to understand the neural signature of various pharmacogenetic associations that have been documented in the literature. This would aid in the development of medications that are targeted to certain genotype groups that have been shown to be more vulnerable to relapse. Novel medications can then be tested using neuroimaging to determine whether neural profiles associated with relapse in high risk groups can be reversed. Neuroimaging could also serve as an early surrogate marker for medication efficacy in Phase II studies and can be effectively utilized prior to conducting costly clinical trials [9].

Several points should be considered in designing such studies. For example, well-validated paradigms that produce robust brain activation should be utilized, since the strength of genetic associations will depend on the refinement of the neural phenotype. Another issue concerns the potential for false positive results of neuroimaging studies, especially when combined with genetics. Due to the relatively small sample sizes in imaging studies, compared to typical genetic association studies, it is important to have an a-priori hypothesis and if possible, utilize functional genetic variants and selection of subjects based on genotype (i.e., to oversample subjects with less prevalent allele). Integrating GWAS approaches with neuroimaging may be valuable to discovery novel genetic variants that correlate with neural phenotypes, although the volume of data generated poses challenges in analysis [106].

Finally, genotyping could be incorporated into studies of the emerging technology, real-time fMRI [33,158]. This approach explores the use of neurofeedback (provided in virtually real-time) to train subjects to modify regional brain activation. Real-time fMRI can be used in conjunction with certain behavioral or coping skills to increase control over cravings for a cigarette or response to cues. Genetic studies may help identify those individuals who are most and least responsive to neuromodulation training although this is very speculative at the present time.

In sum, the integration of genetics and neuroimaging technologies holds promise for improving our understanding of the etiology of nicotine dependence, as well as for accelerating the development and improving the delivery of treatments for nicotine dependence. Such work will benefit greatly from a transdisciplinary team science approach, including attention to emerging ethical and social issues important to consider in the translation of research to practice [122,131].

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