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Mouse models for studying genetic influences on factors determining smoking cessation success in humans

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Abstract

Humans differ in their ability to quit using addictive substances, including nicotine, the major psychoactive ingredient in tobacco. For tobacco smoking, a substantial body of evidence, largely derived from twin studies, indicates that approximately half of these individual differences in ability to quit are heritable [1, 2], genetic influences that likely overlap with those for other addictive substances [3]. Both twin and molecular genetic studies support overlapping influences on nicotine addiction vulnerability and smoking cessation success, although there is little formal analysis of the twin data that supports this important point [2, 3]. None of the current datasets provides clear data concerning which heritable factors might provide robust dimensions around which individuals differ in ability to quit smoking. One approach to this problem is to test mice with genetic variations in genes that contain human variants that alter quit-success. This review considers which features of quit success should be included in a comprehensive approach to elucidating the genetics of quit success, and how those features may be modeled in mice.

Keywords

Nicotine; smoking cessation; quit success; genetics

Introduction

In recent years, some consensus has emerged from genome wide association studies (GWAS) of addiction, and more recently quit success in smoking cessation trials, regarding the nature of the genetic architecture underlying addiction and quit success. As discussed below, these studies have implicated a polygenic architecture in addiction and quit success, and have nominated sets of genes that may underlie addiction and quit success. Demonstration that there are heritable factors that influence individual differences in ability

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to quit smoking does not constitute understanding of how these genetic factors induce their effects. Further examination of these nominated genes is needed in mouse models in which these genes can be purposefully manipulated, but first it is necessary to consider what specific features of addiction, and quit success in particular, should be included in such an approach and which of these can be modeled in mice. Thus, this review addresses aspects of two questions. Firstly, what dimensions should be considered as potential mediators of genetic effects on quit success? This would be based on those dimensions that are: a) known to differ in humans, b) likely to influence success in smoking cessation, and c) likely to display substantial heritable components, at least in humans. Secondly, what are the tests in mice that provide models of variation at loci identified in human GWAS that might be appropriate to detect influences on these specific quit success relevant, heritable dimensions.

A set of dimensions for which there is significant evidence for heritable influences in humans that may be relevant to differences in smoking cessation is provided in Table 1. Thus, some heritable contributions to individual differences in abilities to quit smoking might overlap with some of the heritable contributions to these dimensions. Some of these dimensions come from the literature relating to addictive substances besides nicotine. Many of the theoretical perspectives organizing the dimensions underlying addiction vulnerability are derived from studies using experimental animals. These lines of evidence can inform our understanding of human addiction to nicotine and individual differences in quit-success.

A: Differences in the strength of the dependence prior to the quit attempt: humans

Substantial evidence from family, adoption and twin datasets supports large genetic contributions (approximately 50%) to dependence on addictive substances [3–6]. Most of these data are based on drug dependence diagnoses derived from the Diagnostic and Statistical Manual (DSMIII and IIIR) of the American Psychiatric Association or the Fagerstrom test for nicotine dependence (FTND). Not surprisingly, most of the heritable influence on nicotine dependence overlaps with heritable influences on other substances of abuse [7], with strong data documenting shared heritability for vulnerability to dependence on nicotine and alcohol. Interestingly, FTND items that probe physiological dependence and/or habitual smoking (*e.g.*, time to first morning cigarette) are some of the best predictors of ability to quit. Analyses of genome wide association (GWA) datasets have identified overlapping “pleiotropic” influences of variants at a number of gene loci for vulnerability to dependence and ability to quit (8, 19). In humans, nicotine withdrawal produces a wide range of symptoms, most prominently including restlessness, impatience, anxiety, irritability/anger/frustration, depression/negative affect, difficulty concentrating, impatience and insomnia, while subjective craving, altered nociceptive thresholds, altered neurohormonal profiles, perturbations of learned behaviors, weight gain, decreased heart rate, constipation, and oral/buccal ulcers have also been described (for review see [8–10]). Many of these withdrawal symptoms are likely to be relevant predictors of quit success, although there is only a modest amount of data on this point.

B: Differences in cognition: humans

Substantial evidence from family, adoption and twin datasets supports large genetic contributions to individual differences in a number of mnemonic, and other cognitive,

features [11]. Many of these individual differences in performance on different memory-related tests covary with other aspects of individual differences in general cognitive abilities. It is thus reasonable to assume that some of the substantial genetic influences on memory-associated features might overlap with mnemonic aspects related to smoking cessation. GWA data for CLSTN2, as well as several other addiction related genes, appear to provide direct links between differential effectiveness of nicotine replacement in human smoking cessation and differential effects of nicotine replacement on human individual differences in memory testing during acute nicotine abstinence [12] *(for example, see B3, below)*. It is indeed noteworthy that some evidence suggests that smokers with the most robust cognitive impairments during withdrawal may be at greatest risk for early relapse to smoking during smoking cessation trials [13]. It is likely that there are separable genetic influences on several aspects of human cognitive function involved in nicotine addiction, including premorbid cognitive impairments for which individuals might "self-medicate", memory impairments associated with nicotine withdrawal and the extent to which nicotine withdrawal unmasks underlying cognitive impairments for which nicotine might be compensating prior to withdrawal in humans.

There is modest evidence for nicotine improvements in learning and memory function in nondependent humans, although there is much more evidence for improvements in attentional function (see [14] for review). Thus, nicotine agonists may be useful in the treatment of pre-existing cognitive dysfunctions in smokers, for which they might self-medicate, or for symptoms that emerge during nicotine cessation that may lead to subsequent self-medication and relapse. Although nicotine has been repeatedly linked to cognitive function, the nature of such effects has been attributed to a variety of cognitive processes. There are strong genetic contributions to the cognitive effects of nicotine, baseline differences in cognition in smokers, as well as cognitive deficits associated with withdrawal [15]. Regardless of the nature of such effects, nicotinic agonists have been investigated as treatments for cognitive dysfunctions for a variety of cognitive disorders (see [14, 16]). Even in the absence of a comorbid condition, nicotine withdrawal produces attentional impairments [17], as well as working memory deficits [18], which are ameliorated by nicotine [19], or the $\alpha 4\beta 2$ partial agonist varenicline [20].

In addition to mild premorbid attentional and cognitive impairments that may contribute to smoking in individuals without other comorbid diagnoses, more serious cognitive dysfunctions associated with comorbid psychiatric disorders may especially influence nicotine cessation. The rates of smoking are particularly high in schizophrenia patients [21]. One possible reason for these high rates may be that schizophrenia patients self-medicate for the cognitive deficits that are a core part of the disorder [22], and include a variety of attentional, mnemonic and executive impairments [23–25] that are affected by nicotine and, to some extent, by antipsychotic medications. Along with other deficits, schizophrenia patients have deficits in various forms of sensory gating mechanisms that reflect attentional impairments resulting in "sensory overload", and may thus smoke to alleviate these and other symptoms (for review, see [26]). Smoking appears to normalize some sensory gating deficits in schizophrenia patients [27–29], and some of these effects appear to be dependent on $\alpha 7$ nicotinic subunit containing receptors [30]. Genetic linkage and association studies

have suggested that this gene in particular may be an important determinant of sensory gating deficits in schizophrenia patients [31, 32]. Furthermore, reductions in α7 nicotinic receptor binding have been noted in hippocampal and frontocortical brain regions in schizophrenia patients [33, 34]. Although some of the cognitive problems identified in medicated schizophrenia patients are likely to be due to neuroleptic use, in ways that can be ameliorated by nicotine [35], some of the cognitive deficits in non-smoking schizophrenia patients can be ameliorated by nicotine administration as well [36, 37], suggesting that self-medication for neuroleptic-induced side effects may not explain all smoking by schizophrenia patients. It remains to be seen what proportion of smoking is driven by premorbid conditions and what involves exacerbation of cognitive impairments during nicotine withdrawal, such as working memory deficits, which predict resumption of smoking [13].

In the sections below we approach the problem of individual differences in mnemonic, and other cognitive, features related to smoking cessation success in five ways: (1) differences in the degree to which smoking behavior is conditioned and is habitual; (2) differences in memory impairments associated with withdrawal; (3) differences in rates of extinction that may influence smoking-related conditioned responses; (4) differences in subjective "craving"; and (5) differences in "incubation" features that might enhance responsiveness to nicotine during withdrawal.

B1) Differences in the degree and ways in which smoking was conditioned and is a habit: humans—Although one of the most common complaints among smokers who claim that habit influences ability to quit, the imperative of ingrained habit learning has been little explored experimentally. This lack of information is even more surprising given that several FTND items directly relate to habitual responses that do not involve conscious affective states (such as craving) and appear to be mediated by stimulus-response contingencies. In much of the clinical literature there has been much emphasis on nicotine "craving", particularly as stimulated by smoking associated cues (*see paper by Tiffany and colleagues, this volume*). This issue is discussed in detail below. The "incentive-habit" theory of addiction suggests that after extensive experiences with drugs stimulus-response habits are formed that may be most relevant to later stages of dependence [38]. Such stimulus-response habits are obviously extremely important in smoking. Dependent smokers can amass many more conditioning experiences than individuals who are dependent on other drugs; nicotine dependence may thus provide a paradigmatic stimulus-response addictive habit.

B2) Differences in the memory impairments associated with nicotine withdrawal. Differences in the extent to which nicotine withdrawal unmasks underlying mnemonic impairments for which nicotine might be compensating prior to withdrawal: humans—It is useful to note that, in humans, nicotine withdrawal symptoms appear to depend on the level of nicotine use prior to withdrawal and can vary among individuals in both magnitude and time course, perhaps peaking within the first week of abstinence and tapering off over the subsequent month [39]. Among these symptoms, cognitive impairments have tended to be overlooked, perhaps because many of the

instruments used to assess nicotine withdrawal, such as the SWQ [40], do not assess these symptoms. Alternatively, it appears possible that individuals may lack insight into either their degree of cognitive impairment or this being a reason for their smoking. The large literature on cognitive enhancement in smokers [41] provides little evidence for differences in cognition in non-abstinent smokers, but rather for smoking alleviating a variety of withdrawal-induced cognitive deficits. This statement is not meant to imply that there is not substantial evidence for cognitive, attentional and mnemonic enhancement by nicotine alone, particularly in individuals that show impairments in these functions as a result of a psychiatric conditions (see [14] for review). A more recent meta-analysis [42] found evidence for beneficial effects of nicotine on fine motor performance, response time, alerting attention, orienting attention, short-term episodic memory and working memory. This analysis did not aim to examine abstinent smokers, although smokers can manifest deficits in many of the areas identified. The same group recently reported improvement on a variety of cognitive tasks and mood in abstinent smokers [43]. Indeed, working memory deficits predict smoking resumption following short-term abstinence [13]. Nicotine withdrawal and abstinence have been shown to produce deficits in attention in the Stroop task [44], attention and reaction time in a go-no go task [45, 46], verbal working memory [47] and impairments in a battery of simple cognitive tasks (e.g., digit recall, addition/subtraction) [48]. Interestingly, in that later study, even on tasks in which the subjects' performance was not impaired by nicotine withdrawal, reaction time was increased. Importantly, some of these deficits could be ameliorated by nicotine administration [49], as can a variety of functions in abstinent smokers, including vigilance, divided attention, working memory and sensorimotor function [50]. That study compared nicotine to placebo, not smokers to non-smokers, and although nicotine improves cognition in both smokers and nonsmokers [51], greater impairments in abstinent smokers, combined with experience with these effects, may lead to self-medication.

B3) Differences in the rate of extinction of smoking-related conditioning: humans—Even if no differences exist among smokers in the initial learning associated with tobacco smoking that comes to control behavior, classically and instrumentally, it is possible that individual differences in rates of extinction of these responses may influence smoking cessation. Both self-reports and the clinical literature support the role of conditioned responses in drug-seeking behavior in smokers, whether mediated by conditioned cues that elicit craving or conditioned cues that trigger stimulus response habits. Given these considerations, there have been attempts to develop therapeutic extinction procedures, somewhat analogous to those used in the treatment of other psychiatric disorders, and to augment such approaches pharmacologically. In addiction such approaches have focused on cue reactivity [52], for instance using massed extinction trials with proximal cues [53] or exposure to smoking related contexts [54]. Another, more active, approach is the development of cigarettes with reduced levels of nicotine content. An active extinction procedure in human smokers using denicotinized cigarettes reduced cue-induced responsivity in the amygdala, while increasing responses to control cues [55, 56]. Both denicotinized and nicotine-containing cigarettes ameliorated some of the effects of viewing trauma/stress related imagery in smokers both with, and without, a comorbid diagnosis of post-traumatic stress disorder (PTSD) [57]. The partial NMDA receptor antagonist *d*-

cycloserine also facilitates extinction as revealed by cue reactivity and subjective craving reports [58].

B4) Differences in subjective "craving" identified during and after acute nicotine withdrawal: humans—"Craving" is a self-reported affective state that is used in a number of different contexts, including description of the subjective increase in desire to smoke in abstinent smokers confronted with stressful situations, or exposure to a cigarette or other smoking related cues. Although not all smokers indicate that cue- or stress-induced "craving" mediates relapse, it is certainly a factor in a large number of smokers. The importance of the craving concept is demonstrated by the fact that self-reported craving is a predictor of failure to quit smoking in nicotine cessation trials [59]. Certain medications used for nicotine cessation my act by reducing craving and the cue reactivity that induces craving [60]. The effects of nicotine associated cues are thought to elicit appetitive approach [61], and increase attentiveness towards smoking related cues [62]. Approach elicited by nicotine associated cues and increased attentiveness towards smoking related cues in smokers are consistent with an "incentive sensitization" theory whereby through classical conditioning stimuli repeatedly paired with nicotine (or other drugs of abuse) progressively acquire a greater degree of incentive salience, leading to both approach and attentional biases [63]. However, these responses appear to be greatest in individuals with lower levels of dependence [64]. It has been suggested that incentive salience may play a greater role in individuals with less dependence and that in more dependent individuals control over smoking behavior has become a more automatic, habit-controlled behavior, consistent with the "incentive-habit" theory of addiction [38]. These two theories may not be mutually exclusive, of course, and there may be individual differences in tendencies toward the development of each process so that one process may be more important in some individuals than others.

Nicotine associated cues that have been used to induce craving in human studies include mental imagery [65, 66], pictures [56, 61, 67–69], video [70, 71], smoking paraphernalia [71–73] and even the presence of people smoking [74]. Controlled laboratory stress paradigms also induce craving [66]. Brain imaging studies have associated cue induced changes, and consequent alterations in reported craving, with brain activity in regions of the frontal cortex, temporal cortex, insula, thalamus, nucleus accumbens, amygdala, and hippocampus [67–69, 71]. Expectation of the ability to smoke, after exposure to nicotine associated stimuli, has a large effect on this brain activity [70]. Although not affected by abstinence per se, this same circuitry is associated with craving during abstinence in the absence of overt cues [75]. Furthermore, although these structures no doubt include the neural circuits that underlie craving, the change in activity in individual brain regions produced by cue-induced craving is influenced by dependence, extent of pre-scan withdrawal (craving and negative affect) and sex [55]. Interestingly, impulsivity, which has been suggested to be a predictor of compulsive drug-taking in animal models [76], is predictive of cue-induced craving in smokers [73].

Phenomena associated with craving have a strong genetic basis, as emphasized by the GWA data discussed elsewhere in this article and previous work with individual genes. Human genetic studies have indicated that dopamine system genes affect cue reactivity, including

the dopamine D2 receptor, the dopamine D4 receptor and the dopamine transporter [65, 77]. The dopamine D2 receptor gene has also been implicated in intermediate phenotypes that may play a role in nicotine cessation, including impulsivity [78], and dopamine D2 receptor agonists have been shown to improve working memory deficits [79]. These studies emphasize genes long thought to be important in addiction and the effects of nicotine. As the role of genes implicated by GWAS [80] are examined in animal models, it will be important to examine their expression in the brain regions implicated above, and consequently in different aspects of cue induced craving and other phenomena as implicated by those regional patterns of gene expression.

B5) Differences in possible "incubation" features that might enhance responsiveness to nicotine exposure after a period of abstinence: humans— Incubation is a phenomenon, recently described in animal models, in which sensitivity to stimuli that lead to reinstatement of drug-seeking behavior during a period of forced abstinence (withdrawal) become progressively more potent (for review see [81]). One analysis of the course of drug withdrawal [82] divided abstinence into 3 stages: crash, withdrawal and extinction. In describing the withdrawal phase those authors noted progressive sensitivity to cues eliciting drug craving (similar to the description of incubation in animal models), which subsequently waned, although it did not disappear entirely, during the extinction phase. One of the problems with developing nicotine cessation treatments is that relapse can occur after prolonged periods of abstinence, even after the initial success of nicotine cessation treatments. Rates of relapse in nicotine cessation trials are notoriously high, particularly at longer time periods of abstinence assessment (for review, see [83]). Thus incubation procedures may allow the modeling of this difficult clinical circumstance, in which not only is the clinical goal to produce abstinence, but also to maintain abstinence over long periods of time.

C: Differences in physiologic, nonmenomnic withdrawal signs, such as weight gain: humans

Substantial evidence from human family, adoption and twin datasets supports large genetic contributions to individual differences in vulnerability to obesity [84, 85]. Nicotine may be used for weight control in obesity-prone individuals, and may also emerge as a concern during nicotine withdrawal even for individuals that are not obese. Among the physiological non-mnemonic signs of nicotine withdrawal, loss of the effect of smoking on weight control, and subsequent weight gain, appears to provide a powerful motivation to continue smoking for many smoking women with concerns about weight [86, 87]. It is therefore possible that some of the genetic influences on individual differences in the ability to quit smoking might well overlap with those on individual differences in vulnerability to weight gain, leading to self-medication for weight maintenance. As for other attributes that may lead to self-medication, for weight gain there are also two possibilities: the use of nicotine to treat premorbid tendencies toward obesity and to offset weight gain associated with nicotine withdrawal during quit attempts. Some of the weight gain that follows smoking cessation can be due to increased consumption of more calories, but significant portions may also be due to discontinuation of the enhanced energy expenditures identified in smokers [88]. While we can imagine that some of the genetic influences on individual differences in

ability to quit smoking might overlap with those on individual differences in vulnerability to weight gain or obesity, there is only modest evidence for such overlaps in humans. Other physiologic, non-mnemonic alterations that are observed in nicotine withdrawal include sleep disturbances [89].

D: Differences in the degree to which smoking is driven by stress relief and the degree to which stress exacerbates craving and relapse: humans

Stress may be thought to influence smoking in two ways, based on long-term effects of major stressors (trauma) and acutely in the management of day-to-day stressors. Exposure to traumatic events increases the likelihood of regular smoking and physical/sexual abuse, in particular, is associated with increased nicotine dependence [90]. However, even in the absence of such circumstances individuals may self-medicate. Subjective self reports of "stress" reduction with smoking, exacerbation of stress with nicotine withdrawal, and exacerbation of the likelihood of relapse attributed to "stress" may all be intimately linked to smoking and smoking cessation success. Indeed, one of the most common self-reports of reasons for smoking, particularly in individuals that profess a desire to quit, is failure of abstinence when confronted with stressful circumstances. Indeed, this type of response may relate to certain other psychological features associated with smoking, including both "craving" and habit, which may be driven by stress or consequent negative reinforcement resulting from stress-relief. There is evidence from clinical studies to support these self-reports, including demonstrations that nicotine-associated stimuli alleviate stress [91], and that controlled laboratory stress paradigms induce craving [66]. There are modest amounts of data that support roles for genetic features in individual differences in human self-reported stress.

Additional data support roles for shared genetic determinants for substance dependence and stress-related diagnoses, including PTSD. Furthermore, in both PTSD and non-PTSD smokers, exposure to stressful/traumatic imagery increased nicotine craving, negative affect and PTSD symptoms, and these effects were ameliorated by both nicotine containing and denicotinized cigarettes [57].

E: Differences in affective (or other comorbid) symptoms with withdrawal. The degree to which nicotine is treating underlying affective (or other comorbid) disturbance in smokers: humans

Major affective disorders display substantial heritable factors that are well documented in a large number of studies of bipolar and other major depressive illnesses. Nicotine use in schizophrenia, itself substantially heritable, is so common that a significant number of the cigarettes consumed [92] are used by individuals with this diagnosis [93]. Self-medication of cognitive or other effects related to these psychoses, or their treatment, are commonly held explanations for the disproportionate fraction of smokers who display these diagnoses. Difficulties in quitting could thus be related to these (substantially heritable) diagnoses. Nicotine might medicate symptoms related to the diagnosed condition or its treatment, and/or to ways in which nicotine withdrawal and abstinence might exacerbate features of the comorbid condition, though heritability is less clear for the latter two features. Such a self-

medication hypothesis may also apply to the high use of cigarettes in individuals with bipolar disorder as well [94].

Withdrawal-induced anxiety and dysphoria are common complaints in smokers, although the extent to which these conditions represent premorbid (to nicotine addiction) underlying pathology or consequences of chronic nicotine use is open to question. The role of stress in depressive disorders is also well-known. It appears likely that premorbid affective disorders, or the exacerbation of such symptoms by withdrawal, could be important factors that influence nicotine cessation in these individuals. Nicotine use is higher in individuals with depression [95]. These individuals have increased failure in nicotine cessation trials [96], which might be linked to exacerbation of dysphoric symptoms and relapse of depression [97], or cognitive deficits associated with depression [98]. Indeed, nicotine improves spatial working memory deficits in abstinent smokers, although this effect has been reported to be influenced by allelic variation at the serotonin transporter locus [99]. Even in individuals not diagnosed with depression, withdrawal-induced dysphoria is ameliorated by nicotine [43].

Other comorbid conditions may also influence predisposition to initiate smoking, the progression toward addiction, or aspects of cessation. In addition to the greatly increased incidence of smoking in schizophrenia patients that was discussed previously, attention deficit hyperactivity disorder (ADHD) has also been suggested to influence smoking and smoking cessation (for review, see [100]). As that review discusses, the core symptoms of ADHD, deficits in attention, inhibitory control and social functioning, and impulsivity and sensation seeking, suggest mechanisms by which ADHD might affect different stages of the addictive process. Indeed, adolescents with ADHD are more likely to initiate smoking [101] and the comorbidity of smoking in adults with ADHD is 42% [102]. Interestingly, in the latter study the quit ratio (ratio of ex-smokers to ever-smokers) in individuals with ADHD was 29%, compared to 49% in the general population. Furthermore, retrospectively reported ADHD symptoms are associated with the progression of nicotine addiction and dependence in current smokers with ADHD [103]. Furthermore, abstinence-induced increases in response inhibition errors, a measure of trait impulsivity, are positively correlated with baseline plasma cotinine and boredom susceptibility in smokers [104]. Abstinence also affects reaction time in a continuous performance task and these effects can be ameliorated by smoking [105]. Candidate gene approaches identified few genes of major effect associating ADHD with nicotine addiction [106], including the dopamine D2 receptor. There were several other effects that approached significance, however. Given the genetic architecture for addiction discussed in this review, it might be presumed that GWA approaches may be more successful in identifying such relationships.

F: Individual differences in delayed discounting: humans

Initial twin study data support significant heritability of components for individual differences in delayed discounting, even when assessed in adolescence. Such findings indicate overlap between the genetic mechanisms underlying delayed discounting and genetic mechanisms underlying substance dependence. Impairments of delay discounting in smokers have been associated with both impulsivity and cue-induced craving [73], although smoking-related cues do not produce additional impairments in delay discounting [74].

Molecular genetic studies of smoking cessation: humans

Candidate gene association and GWA approaches have now assembled a large amount of data comparing multiple samples of successful and unsuccessful tobacco quitters. Many of these samples are of modest size, and many compare individuals who successfully quit smoking in the context of carefully monitored clinical trials to those who are not able to quit. The trials that have been assessed to date have largely used nicotine replacement, replacement of standard cigarettes with denicotinized cigarettes, and the dopamine transporter blocker bupropion, that also displays binding potency at a subset of nicotinic receptor subtypes [107–121]. In other studies, GWA methods have been applied to individuals who report that they continue to smoke in comparison to those who report smoking in the past but having attained and maintained abstinence.

These association studies provide no evidence for genes in which individual variants are likely to exert any large effects on ability to quit. These studies have identified sets of genetic markers that can help to prospectively predict ability to quit when applied to subsequent clinical trials [107, 122]. These association studies also nominate a number of genes that are strong candidates to contain variants that influence abilities to quit smoking. The most robust data comes from genes that are identified by multiple studies of both smoking cessation and addiction vulnerability. Variation at these genomic loci is likely to provide variation in one or more of the features noted above that lead to individual differences in ability to quit.

Animal models for features related to smoking and quit success

Reviews by Markou and colleagues [122, 123] describe animal models that focus on 1) acquisition/maintenance, 2) nicotine reinforcement, 3) motivation to consume nicotine, 4) neuroadaptations occurring during the development of nicotine dependence, 5) nicotine withdrawal, and 6) drug seeking that has high relevance to relapse. Many of these features are tied to human genetic influences on drug dependence, as discussed above. Most of these procedures were developed in rats, prior to the consideration of genetic manipulations in mice as a way to approach the genetic basis of psychiatric conditions. While an increasing number of genetically modified rat strains are now available, these are currently quite limited compared to the number of available mouse models, and the rat genome is still far less complete than the mouse genome. Thus, the sophistication and depth of understanding of rat genetic models is dwarfed by the depth and sophistication of understanding of the mouse genetic models. Thus, in this review we focus on behavioral models available in mice that will be useful in elaborating the genetic basis of smoking cessation.

Outlined above are those features of tobacco smokers, either pre-existing or those resulting from chronic nicotine administration or nicotine withdrawal, that need to be considered in any comprehensive approach to the genetics of smoking and quit success. In genetic comparisons of smokers and non-smokers, or quitters and non-quitters, GWAS have identified a large set of genes that appear to contribute to these features; however, although contributing to these general features overall, individual genes are most likely to be involved in more specific processes upon closer inspection. Thus, when trying to model these genetic

differences in mice using transgenic manipulations it is necessary to create a battery of tests that assesses as many of these features as feasible. Although other information (e.g., the distribution of gene or protein expression, knowledge about the function of the gene) may lead us to think that certain genes participate in particular processes, it would nonetheless be informative to examine transgenic models in a variety of behavioral models to demonstrate the specificity of the effects of those manipulations, and by implication the role of those genes in nicotine addiction or nicotine cessation.

A: Mouse models for differences in the strength of the dependence prior to the quit attempt

A number of approaches to modeling dependence in animal models of addiction have been taken. With regard to nicotine, most investigations have concentrated upon either physical dependence expressed as somatic signs of withdrawal upon cessation of nicotine, or excessive consumption in self-administration models. However, more recent approaches have suggested that it is not the level consumption that best represents dependence, but rather certain features of that consumption. Other models involve assessment of the anhedonic (e.g. [124]) and aversive (e.g. [125]) aspects of nicotine withdrawal.

Physiological dependence on nicotine is readily demonstrated in mice which have been repeatedly/chronically treated with nicotine and then withdrawn from nicotine. Acute adaptations to nicotine application can also be readily demonstrated in mouse and/or rat nicotinic receptors, with nAChRs with alpha4/beta2 and alpha 7 subunit homomeric receptors most studied in a variety of *in vitro* and *ex vivo* settings (e.g. [126]). There is substantial evidence for tolerance and dependence in whole animals treated with long term nicotine regimens. Protocols that have been used to produce physiological dependence include twice-daily intraperitoneal injections, osmotic pump infusions over 1–4 weeks, and oral nicotine self-administration. After these chronic nicotine treatments, physical dependence can be demonstrated, since withdrawal syndromes develop during abstinence after discontinuation of nicotine administration or administration of partial or full nicotine receptor antagonist administration. In mice tolerance can be measured to the effects of nicotine on locomotion, rearing, motor coordination, startle, temperature, heart rate, and operant responding for food reinforcement [127–131]. The rate and extent of tolerance varies across outcomes and also differs among mouse strains [128, 129]. Interestingly, although somatic withdrawal symptoms were largely eliminated in α7 nicotinic receptor subunit knockout mice, tolerance to the locomotor effects of nicotine was unaffected [132, 133]. The neurobiological basis of physiological dependence may be quite different from that mediating other aspects of tolerance, withdrawal and dependence, especially since there are reports that, at least in rats, the somatic signs of nicotine withdrawal are primarily centrally mediated [134]. Mice can be tested for negative features associated with drug administration and withdrawal using several procedures. For example, Damaj and colleagues [125] evaluated mice 18 – 24 h after removal of osmotic minipumps that administered approximately 36 mg/kg/day nicotine for 2 – 4 weeks. An experimental sequence of: 5 min evaluation in the plus maze test for anxiety-related behavior, 20 min observation of somatic signs measured as paw and body tremors, head shakes, backing, jumps, curls, and ptosis, followed in turn by hotplate and tail-flick nociception/analgesia

testing to evaluate hyperalgesia, allowed a robust characterization of somatic signs and symptoms of nicotine withdrawal. Testing for mouse models of the dysphoric aspects of human nicotine withdrawal has focused on findings from conditioned place avoidance and conditioned taste aversion, and alterations in brain stimulation reward thresholds discussed in subsequent sections. However, the question remains as to whether these tests incorporate those features of withdrawal that are most relevant to nicotine dependence and nicotine cessation. Spontaneous withdrawal is also associated with somatic signs of withdrawal, increased anxiety, and hyperalgesia [124, 135, 136], effects which are separable from conditioned effects of nicotine [125]. Mouse models assessing the dysphoric aspects of human nicotine withdrawal have focused on procedures that examine subsequent conditioned responses to stimuli associated with nicotine withdrawal, discussed in a subsequent section. Of more direct relevance to the hedonic state during withdrawal, it has been shown that nicotine withdrawal elevates brain stimulation reward thresholds [124, 137].

In considering the best way to define dependence in an animal model one approach is to consider the items that define nicotine dependence in the FTND and DSM-IV [138, 139]. Several of the DSM-IV nicotine dependence criteria provide construct validity for mouse tests of tolerance and physical dependence, in ways that are noted below. These include: “Withdrawal, as manifested by…..the characteristic withdrawal syndrome for the substance” and “Tolerance, as defined by… diminished effect with continued use of the same amount of the substance”. There are several approaches to identifying these characteristics, including examination of chronic nicotine exposure, evidence of physiological dependence and withdrawal.

Other features contributing to FTND criteria for nicotine dependence that are demonstrated readily in mouse models appear to provide strong construct validity, including avid self-administration that mice can demonstrate after periods during which access to nicotine is restricted. This sort of data appears to provide construct validity based upon at least three of the six total FTND questions, for which responses can provide half of the total possible FTND score: “How soon after you wake up do you smoke your first cigarette?”, “Which cigarette would you hate most to give up? The first one in the morning? All others?”, and “Do you smoke more frequently during the first hours after waking than during the rest of the day?”. It is interesting to note that the “How soon after you wake up do you smoke your first cigarette?” FTND item provides one of the best clinical predictors of ability to quit smoking. The other FTND item for which there is good construct validity in rodent models assesses smoking quantity/frequency: “How many cigarettes/day do you smoke?”. Mice can self-administer nicotine in a number of relatively specific experimental procedures that examine specific psychological features of drug-seeking behavior. There is only modest data that supports mouse dosing regimens that reliably provide the plasma nicotine levels provided by the < ½ pack/day, 1 – 1 ½ pack/day and > 1 ½ packs/day human cut offs for FTND ratings [140]. Nevertheless, the dose response relationship implicit in these cutoffs provides only a 3–4 fold dosing range. This relatively limited range of rewarding nicotine doses is concordant with the steep, inverted U-shaped dose response relationships noted in

mouse studies of several different nicotine-mediated effects (*see below*) including self-administration.

Mouse models for features of other measures of dependence, as used in some of the DSM-IV nicotine dependence criteria and some of the FTND score criteria, might display lower levels of construct validity. The DSM [141] criterion "A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period…a) There is a persistent desire or unsuccessful efforts to cut down or control substance use… substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance". This DSM criterion provides construct validity for the FTND items: "Do you smoke when you are so ill that you are in bed most of the day? And "Do you find it difficult to refrain from smoking in places where it is forbidden?", but are less well addressed in current mouse models. Recent suggestions concerning those features of self-administration studies that may better model these features are discussed below, but have not yet been applied to mouse studies.

Thus, many of these criteria for dependence relate to nicotine consumption, which has primarily been addressed using two methods: intravenous self-administration and oral self-administration. One of the factors thought most to contribute not only to whether a drug is consumed initially, but also to how much is consumed, is the strength of reinforcement, which is readily measured in self-administration paradigms. On the simplest level, when considering control of drug-seeking behavior by the reinforcing effects of drugs of abuse, the opposing effects of reward and aversion, eliciting approach and avoidance respectively, must be considered. Operant self-administration represents this approach-avoidance conflict in an obvious way, whether the drug is sought by pressing the lever, or avoided by not pressing the lever, although simpler approaches have been taken.

Locomotor stimulation and the sensitization of locomotor stimulant effects of drugs of abuse are hypothesized by some authors to represent approach to rewarding cues (e.g. drug seeking behavior) [142]. However, although nicotine produces both locomotor activation and inhibition, it often produces locomotor inhibition in mice (e.g. [143, 144]). Tolerance develops to these effects with repeated treatment [145], which can subsequently reveal locomotor stimulant and sensitized responses to nicotine [146, 147]. Under these circumstances it is often uncertain to what extent "sensitization" of locomotor responses to nicotine reflects tolerance to locomotor inhibition or sensitization of locomotor stimulant responses. Nonetheless, in mouse lines selected for nicotine-induced locomotor activation or depression to 0.75 mg/kg s.c. nicotine, nicotine produced conditioned place preferences and aversions in the lines that were activated and inhibited by nicotine respectively [148], consistent with the hypothesis that locomotor stimulant and reinforcing effects of nicotine share some common mechanisms.

Behavioral sensitization models have a substantial conditioned component, although many procedures do not necessarily separate context-dependent and context-independent effects (that is, conditioned and non-conditioned forms of sensitization). Twice daily nicotine (0.05

mg/kg s.c.) induces sensitization in a procedure in which most of the injections were in the home cage, and presumably less context-dependent [149], but nicotine sensitization was also observed in a procedure that was likely to be mostly context-dependent [150]. Interestingly, in that study nicotine did not produce locomotor stimulation on the first day, but did by the second day. There are substantial genetic contributions to the locomotor effects of nicotine [128, 129, 151], that are likely due to regional differences in nicotine receptor binding [152]. Specific gene manipulations also affect nicotine locomotor sensitization [149, 153].

Forced oral nicotine consumption, a procedure often used to induce tolerance, dependence and withdrawal, results in increased locomotion and tolerance to the locomotor depressant effects of nicotine [154]. Animals in a free choice drinking situation also show increased locomotor activity, however [155]. Without tolerance to the locomotor depressant effects of nicotine, quite low doses of nicotine are sometimes needed to produce locomotor activation in mice, when it is observed [156]. Chronic home cage exposure to oral nicotine produces enhanced locomotion after a period of time [157] in ways that are dependent on dopamine and β2-containing nicotinic receptors [158]. Low doses of nicotine also decrease anxiety in the mirrored chamber [159], and the elevated plus maze [160], at doses that increase locomotion in the plus maze.

Although a variety of nicotine mediated phenomena can be examined using locomotion, the primarily locomotor depressant effects of nicotine in naïve mice are limiting. Intravenous self-administration has been most often used to model drug-seeking behavior and increased propensity towards drug-seeking has been thought to model dependence. However, nicotine has a particularly short half-life in mice [161], which may have an impact on a variety of behavioral procedures, including intravenous self-administration, requiring higher nicotine doses, and more frequent administration, to reach plasma levels typical of rats [162]. In addition, the doses that produce rewarding and aversive responses to nicotine are quite close, making the effective dose range for intravenous self-administration (and many other nicotine-induced behaviors) quite narrow. The dose-range for i.v. nicotine self-administration in mice is between 0.01 and 0.25 mg/kg [163, 164], although as is the case for nicotine conditioned place preferences, in any particular study the range of effective doses varies (e.g. [165–167]). This narrow range can make it difficult to initiate nicotine self-administration, and generally speaking operant responding for nicotine is not as robust as for other drugs of abuse [164]. For this reason it is common to train animals to respond for food, or even cocaine, prior to nicotine [168]. A recent study [169] characterized a variety of key parameters that facilitated nicotine self-administration in mice: prior training for food reward, initial exposure to low i.v. nicotine doses, a slower rate of drug delivery, priming infusions, testing in darkness, and testing at consistent times every day. Under these conditions mice self-administered nicotine on more demanding schedules, over a broader range of doses, more robustly (comparing the active and inactive levers), and would switch responding between levers if the contingencies were changed (see also discussion in [170]). In addition, mice from many transgenic strains are substantially less robust than their wildtype counterparts, often for reasons that are not well understood, and consequently die when being cannulated for venous access, develop clots in intravenous catheters more frequently, and are likely to experience greater physiological stress along with these deleterious outcomes (e.g. [171]).

Given the narrow range of doses that are self-administered by mice, both the rewarding and aversive effects of nicotine may thus be important determinants of nicotine self-administration. For instance, a recent analysis found a substantial widening of the effective dose range for nicotine self-administration in α5 nicotinic receptor subunit knockout mice [172], with a substantial increase in responding for higher nicotine doses suggesting reduced aversive effects of nicotine in these mice. These effects appeared to be dependent on medial habenular α5 expression as the wildtype phenotype, a narrower dose range, could be rescued by virally mediated medial habenula α5 expression in knockout mice. Similarly to what is observed for intravenous nicotine self-administration, although low doses of nicotine produce lowering of intracranial self-stimulation (ICSS) thresholds, higher doses produce elevations in ICSS thresholds [172, 173].

Another approach to separating the rewarding and aversive effects of nicotine is direct intracerebral injection of nicotine into discrete brain sites that differentially modulate the aversive and rewarding effects of nicotine. An interesting series of studies used a novel distinct trial self-administration procedure in which mice received injections of nicotine by entering one arm of a Y maze (or saline by entering the other). Self-administration, under these conditions, was dependent on α5 nicotinic receptors in the ventral tegmental area [174]. Using the same procedure, gene knockout of the α4, but not the α6, nicotinic receptor subtype reduced intracranial self-administration directly into the ventral tegmental area [175], as well as nicotine-induced dopamine neuron burst-firing. Another study suggested that intracerebral nicotine self-administration in the ventral tegmental area was dependent on dopamine D1 receptors in addition to nicotinic receptors [176].

Although self-administration procedures model drug-seeking behavior, these procedures do not necessarily model drug dependence very well – at least if the only consideration is the rate of acquisition and sensitivity to reinforcement. In recent years several features of self-administration procedures have been suggested to have relevance to drug dependence. Although high reactivity to novelty predicts initiation of cocaine intake in rats [76], impulsivity predicts high rates of cocaine intake [76, 177]. Importantly, impulsivity predicts features of drug taking in self-administration procedures that model dependence [76]: (1) persistence of drug taking in the face of negative consequences, (2) increased motivation toward drug-seeking, and (3) inability to refrain from drug-seeking. These features were operationally defined as (1) operant responding for cocaine during a concurrent punishment schedule, (2) a progressive ratio breakpoint, and (3) responses during an extinction session. These criteria have yet to be assessed for nicotine self-administration or in mice.

One additional problem with the validity of i.v. nicotine self-administration is that this is not a method by which humans self-administer nicotine. An alternative is voluntary oral nicotine consumption using a standard home-cage 2 bottle choice design [178–185]. In most of these studies nicotine was consumed in concentrations between 1 and 100 μg/ml, with distinct reductions at higher concentrations, similar to conditioned place preference (see below) and intravenous self-administration. These reductions at high nicotine concentrations appear to be strain-dependent, as C57BL/6J mice drink more nicotine overall and show less reduction in consumption at higher concentrations than other mouse strains [179]. Oral nicotine consumption in mice has been shown to produce blood levels of nicotine similar to those

seen in human smokers [186]. Another important consideration in such studies is the duration of exposure to nicotine. For instance, in a study of long-term (5 months) oral nicotine consumption [184], gene knockout of the β2 nicotinic receptor subunit led to a decrease in nicotine consumption during the first few weeks of the study, but subsequently the consumption of these mice did not differ from that of wild-type mice. By contrast, α7 nicotinic receptor subunit knockout mice did not differ from wild-type mice initially, but did so later in the study.

Some studies have also used forced oral nicotine consumption procedures, in which nicotine solutions are the only fluid source [187, 188]. These procedures generally involve induce high nicotine consumption and dependence, defined here by the occurrence of withdrawal symptoms during forced or precipitated abstinence. The levels of nicotine that are consumed in voluntary and forced consumption procedures can be quite high, comparable to those observed in human smokers [187]. Moreover, in both the voluntary and forced consumption procedure, the pattern of drinking is similar to human nicotine consumption in which frequent, small doses are taken during the active part of the diurnal cycle. However, the lack of an operant component limits the assessment of other behavioral features as discussed above.

B1) Mouse models for differences in the degree and ways in which smoking is conditioned and is a habit

When smokers are asked about what behavioral responses impair their ability to successfully quit smoking, two of the most common answers involve responses to conditioned cues (e.g. craving) and inability to refrain from highly habitual behavior. The development of these types of responses involves learning about stimulus-reinforcer and stimulus-response contingencies, respectively. With regard to nicotine, opposing effects of nicotinic receptors in different brain regions can produce diverse rewarding and aversive consequences that influence these processes, such that small differences in the balance of these interactive effects can produce large differences in the initial and subsequent behavioral consequences of nicotine [189]. Conditioned aversive and rewarding effects of nicotine are dissociable experimentally, even though they are experienced simultaneously by smokers. Certain aspects of conditioned responses to nicotine have been extensively studied and modeled in mice, while others have been largely ignored; habit learning has only recently been modeled in mice.

Using the conditioned place preference (approach) and avoidance procedures that model separate aspects of drug-seeking related to the conditioned incentive-approach properties of nicotine, as well as the conditioned incentive-avoidance properties of nicotine withdrawal, separate brain regions, the insula and orbitofrontal cortex respectively, have been shown to be separately and dissociably involved in these processes [190]. However, the most commonly used approach to examine conditioned responses to nicotine are the conditioned place preference (CPP) and conditioned place avoidance (CPA) procedures, that have been commonly used to measure the incentive properties of many drugs of abuse [191]. In practice such procedures do not separate the rewarding and aversive properties of drugs, nor do self-administration procedures, but because the dose ranges for drug reward and aversion

are typically different they can be effectively separately accessed in dose response studies in terms of the ascending and descending limb of the conditioned place preference dose response curve. However, many early attempts had difficulty demonstrating nicotine CPP because the Effective Doses (ED) 50 for the rewarding and aversive effects of nicotine are close to each other. Subsequently, mouse studies were able to consistently demonstrate nicotine CPP over a narrow dose range [182]. For example, an early study found that 0.5 mg/kg IP nicotine base would induce a CPP, and 2.0 mg/kg induce a conditioned place aversion (CPA), while 1.0 mg/kg was without effect, presumably due to combined rewarding and aversive effects of nicotine [192]. A “biased” place preference procedure has generally been found to produce more robust and consistent CPP, and this does not seem to be related to reduced aversion [193]. Nonetheless, “unbiased” procedures have also been shown to produce nicotine CPP [181]. Studies in mice have generally found that nicotine doses of 0.5 to 1.0 mg/kg i.p. or s.c. are rewarding, while doses above that do not produce CPP or produce CPA [135, 156, 185, 194–198]. However, the particular dose range that successfully produces CPP varies substantially from study to study, and it is common within a study for only a single dose to produce CPP. The factors that determine which dose is efficacious in producing CPP are numerous and include strain [199], age [195], sex [200] and prior handling [194]. In mice, a dose of 1.0 mg/kg s.c. may (e.g. [201]) or may not (e.g. [135]) produce a significant CPP, while doses above 1.0 mg/kg generally produce a CPA (e.g. [201]). Although it is important to carefully characterize the dose-response relationship to identify the CPP-CPA spectrum in each experimental circumstance, the technique can be effectively used to identify genetic differences [202], including a complete shift in the spectrum of rewarding and aversive effects of nicotine in fosB knockout mice [182]. Conditional knockout of NMDA receptors in dopamine neurons has also been shown to eliminate nicotine CPP [203]. Nicotine doses that produce CPP generally correspond with those that produce elevations in extracellular dopamine levels in the nucleus accumbens [135]; higher doses that do not produce CPP also fail to increase dopamine levels. Several recent genetic effects on nicotine CPP have been shown to have specific effects on the descending limb of the nicotine dose-response relationship for CPP [204].

The aversive effects of nicotine can also be measured in the conditioned taste aversion (CTA) procedure where nicotine, generally, produces a robust CTA [192, 205, 206]. However, certain mouse strains appear to be less sensitive to the aversive effects of nicotine in this procedure, including C57BL/6J, BALB/cJ and CD-1 mice [192, 207]. The development of a CTA requires quite high doses, 2.0 mg/kg s.c., freebase or more. These doses are near to those that will induce seizures [208]. Analgesic effects of nicotine also occur at high nicotine doses, over 3 mg/kg s.c. [135]. Although nicotine withdrawal produces a variety of aversive effects discussed in a later section, nicotine withdrawal does not lead to CTA [209], although conditioned aversive effects of nicotine withdrawal have been observed in other procedures (see above). Stimuli associated with nicotine withdrawal elevated ICSS thresholds in rats [210], an effect that could be described as *conditioned* withdrawal induced dysphoria. The aversive state associated with mecamylamine-precipitated nicotine withdrawal conditions place avoidance [136], which is κ opioid receptor dependent. This involvement of κ opioid receptors in CPA is in contrast to nicotine CPP, which is μ opioid receptor dependent [197]. The somatic withdrawal signs are also

largely dependent on preproenkephalin [135]. Spontaneous withdrawal from chronic nicotine infusion with minipumps can also produce a CPA, but this is dependent on time, observable at 8 hours post withdrawal, but not at 4 or 12 hours postwithdrawal [211]. These effects were dopamine dependent. Furthermore, acute high nicotine doses induce a CPA, but conditioning 8 hours after receiving the same dose induces a CPP [211]. These studies illustrate that nicotine withdrawal states must be considered in terms of rewarding and aversive opponent processes that are only partially dopamine dependent and have different time-courses [212]. Chronic forced oral nicotine consumption (200 μg/mL nicotine, 0.33% saccharin in drinking water for 14 days) can also be used to induce dependence as evidenced by mecamylamine-induced withdrawal conditioned place aversion [190]. In an interesting procedure, Scott and Hiroi [213] paired a tone with mecamylamine-induced withdrawal and then used that tone to reinstate nicotine CPP, the interpretation being that the anticipation of withdrawal elicited drug seeking behavior, which was dormant (extinguished) by a long delay between nicotine conditioning and place preference testing.

Acute or chronic nicotine exposure and nicotine withdrawal may have different effects depending upon the age at which the nicotine exposure and withdrawal occur, including gestational [214] and adolescent exposure [195, 215, 216]. Some age effects may be the result of differences in nicotine metabolism [187]. These factors have not been fully considered in studies of the conditioned effects of nicotine, but are obviously of great importance given the potential for differences in responsivity to nicotine in adolescents, the age at which smoking is usually initiated. As the studies discussed above indicate, conditioned responses to stimuli associated with nicotine and nicotine withdrawal that drive goal-directed behavior have been extensively studied in mice. However, other procedures, that involve other reward-related processes, have not yet been applied extensively to studies of nicotine responses in mice.

Several important models that had previously been developed in rats have recently been operationalized in mice, including Pavlovian to instrumental transfer (PIT), cue-induced reinstatement and habit learning. In PIT a classically conditioned stimulus energizes instrumental responding [217]. Indeed classically conditioned stimuli usually contribute to the vigor of instrumental responding in most standard self-administration procedures. PIT obviously models some aspects of craving, and has parallels to cue-induced reinstatement of operant responding for drug reward [217, 218]. As in humans [219], classically conditioned cues, stress and drug priming can reinstate drug seeking in mice [220], although interestingly conditioned cues were far more effective in that study. The acquisition of habit-based learning is thought to reflect highly over-learned, automatic responses that have become dissociated from immediate feedback from reinforcement, such that responding is not affected by reinforcer devaluation. This procedure has been recently demonstrated in mice [217], but has not yet been applied to nicotine studies.

B2: Mouse models for differences in the memory impairments associated with nicotine withdrawal and differences in the extent to which nicotine withdrawal unmasks underlying mnemonic impairments for which nicotine may be compensating

It is likely that there are influences of both the extent to which there are premorbid memory impairments in smokers, memory impairments precipitated by nicotine withdrawal and the extent to which nicotine withdrawal unmasks premorbid mnemonic impairments for which nicotine might be compensating, on nicotine cessation. All of these possibilities are discussed below, including the effects of acute nicotine on cognition that might lead to self-medication. However, the demonstration of self-medication in experimental animals, though possible has not been applied to many of the effects of nicotine, and may not be able to model this aspect of nicotine addiction in all respects.

Behavioral genetic studies in mice provide a way to evaluate the precise contributions that genetic differences may make to specific cognitive processes that contribute to nicotine addiction and cessation. Nicotine affects a variety of cognitive processes through different mechanisms, involving different brain regions. It appears that nicotine especially affects hippocampal dependent learning (for review, see [221]). Specific nicotinic receptors within specific parts of the hippocampal circuitry are positioned to affect long-term potentiation and hippocampal plasticity [222, 223], and consequently a variety of learning and memory processes. Not surprisingly, given the multiplicity of nicotine effects on learning and memory, the effects of nicotine in studies of learning and memory are dependent on specific task demands. Even in quite similar procedures, nicotine dose, the chronicity and timing of treatments, and characteristics of the subjects (e.g., strain, sex, age). In the Morris water maze acute nicotine administered during acquisition produced impairments in spatial learning [224]. However, a previous study found that although acute treatments during training only produced learning impairments, a regimen that began 5 days prior to training, and continued throughout acquisition, resulted in improved spatial learning [225], although another study did not find improvements under those conditions [226]. The factors contributing to whether or not nicotine produces improvements in learning or memory in the water maze no doubt include many of the factors mentioned above. A rather important factor may be premorbid impairment, as suggested by the fact that cued and spatial learning impairments in the Morris water maze in dopamine transporter knockout mice is improved by nicotine [227]. It is interesting to note that the dopamine transporter knockout mouse has been considered to be an animal model of schizophrenia and the incidence of tobacco smoking is high in schizophrenic patients (as discussed above).

The procedure that has been most often used to examine the effects of nicotine on learning and memory is an aversive conditioning procedure that assesses delay cue conditioning, as well as hippocampal dependent contextual conditioning [228]. In this procedure, nicotine has consistently been shown to enhance contextual fear conditioning when injected both during acquisition and expression [228–238], but not delay cued fear conditioning [228, 232–238]. Interestingly, although nicotine had no effect on delay cued fear conditioning in those experiments, nicotine increases trace cued fear conditioning [239, 240]. Like contextual conditioning, but not delay cued fear conditioning, trace cued fear conditioning is hippocampal dependent [241]. Although in these studies nicotine was given both during

acquisition and retrieval, the strong discriminative stimulus properties of nicotine or other state-dependent effects are not thought to be important in producing these effects [230]. Indeed, assessment of conditioning one week after an initial expression test revealed increased contextual conditioning even though no nicotine was administered at that time [231]. Nicotine has other effects on learning at higher doses, including impairment of contextual conditioning [228, 232]. Injections of nicotine into the dorsal hippocampus improve contextual fear learning [237, 242], but again have no effect on delay cued fear conditioning. Nicotine injections in the medial prefrontal cortex or dorsal hippocampus improves trace cued fear conditioning, while ventral hippocampal nicotine injections impair both contextual and trace cued fear conditioning [243]. These effects on both contextual conditioning and trace cued fear conditioning are dependent on β2 nicotinic containing receptors [240, 244], while nicotine-induced enhancement of passive avoidance is lost in β2 nicotinic receptor subunit knockout mice [245]. Finally, the context pre-exposure facilitation effect procedure has been used to separate the two aspects of contextual fear conditioning, learning about the context and associating the context with the unconditioned stimulus. In this procedure, nicotine was found to enhance contextual learning but not associative learning [246].

Nicotine improves learning in a variety of other tasks as well, including aversively motivated discrimination learning [247, 248], passive avoidance [249, 250], inhibitory avoidance [251], social recognition [252], transfer of aversive conditioning [253] and open arm avoidance learning in the plus maze [254]. Consistent with these effects of nicotine, and a broad role of acetylcholine in learning, spatial discrimination is impaired in both α7 and β2 nicotinic receptor subunit knockout mice [184], although another study found no effect of α7 nicotinic receptor subunit gene knockout on spatial learning in the Morris water maze [255]. Consistent with the first study, elevating α7 nicotinic receptor subunit expression in the hippocampus by viral gene delivery enhances spatial learning [256]. Nicotine also improves pharmacologically or aging-induced learning deficits [257–260] and some of these effects also involve the dorsal hippocampus [261]. Using knockout mice, both α7 and β2 nicotinic receptor subunits, but not β3 or β4 receptor subunits, have been found to be involved in contextual learning, improvements in contextual learning produced by nicotine or the reversal of ethanol-induced impairments in contextual learning by nicotine [232].

Although many of the effects of nicotine discussed above are hippocampally mediated, other effects of nicotine are mediated by other brain structures. For instance, nicotine injected into the anterior cingulate improved learning of the plus-maze discriminative avoidance task [259], and impairments in contextual and cued fear conditioning produced by ethanol were reversed by nicotine injections in the anterior cingulate [242]. More specific nicotinic agonists have been reported to improve aversive conditioning, inhibitory avoidance, social recognition memory, object recognition and working memory, either under baseline conditions or by reversing pharmacological or age-induced impairments [252, 258, 262–269]. Many of these effects are highly strain dependent, and in the strains in which they are observed, higher nicotine doses may produce impairments [248]. Using an odor span working memory task, impairments of working memory have been demonstrated in human caspase 3 over-expressing transgenic mice [270], despite no deficits in other aspects of olfactory learning, which were reversed by nicotine administration.

Few studies in mice have specifically addressed the issue of nicotine effects on memory consolidation, although the short duration of nicotine action may limit learning effects mediated by enhanced memory consolidation. Nicotine has been shown to improve consolidation of an aversively motivated task [248] and transfer of aversive conditioning [253], but effects on consolidation are not always observed [231]. Nicotine has also been suggested to specifically affect memory retention, albeit only in mice that were poor learners to begin with [271] and improves memory retrieval in a passive avoidance task [272]. Nicotine effects on retrieval are likely to be involved in nicotine enhancement of contextual conditioning since nicotine is usually administered both during acquisition and expression.

The studies discussed above involve acute administration of nicotine to naïve animals. However, chronic administration, and administration during withdrawal, will probably be more relevant to nicotine administration in dependent individuals. Chronic nicotine administration and administration during withdrawal has been shown to produce a variety of effects on cognition in mice. For instance, chronic nicotine administration ameliorates stress-induced impairments in spontaneous alteration [273] and spatial learning deficits in the Morris water maze produced by prenatal barbiturate exposure [274]. Opposite to the generally beneficial effects of acute nicotine on contextual conditioning, spontaneous nicotine withdrawal impairs contextual conditioning, but not, contrary to what would be expected from the acute effects of nicotine, delay cued fear conditioning [234, 240, 269, 275, 276]. Again, these techniques have proven useful to probe the genetic basis of nicotine effects on cognition. The effects of nicotine withdrawal on contextual conditioning are not observed in β2 nicotinic receptor subunit knockout mice [275], suggesting the importance of this receptor in this process. Acute nicotine treatment reversed the impairment produced by nicotine withdrawal on contextual fear conditioning [234], as do other putative or current nicotine cessation treatments, including bupropion [277], varenicline [278] and galantamine [279]. The deficit in contextual fear conditioning has been compared to cognitive deficits in attention deficit hyperactivity disorder and could also be reversed by atomoxetine [280]. Precipitated nicotine withdrawal with the high-affinity nicotine receptor antagonist dihydro-β-erythroidine impairs acquisition of trace [240] and contextual [244] fear conditioning, although spontaneous withdrawal obviously has more etiological validity for nicotine cessation in humans.

Improvements in learning produced by nicotine may involve alterations in several aspects of cognitive function. Indeed there may be more evidence for improvements in attentional function, that in mnemonic function (see [14] for review). In mice, visuospatial attention has been studied using the 5-choice serial reaction time task (5CSRTT; [281]). In this task, brief visual stimuli must be detected across 5 spatial locations, assessing sustained and divided attention. An important aspect of this, and similar, procedures is to increase attentional load by altering the predictability of the stimulus by changing the inter-trial interval, or decreasing the stimulus intensity or duration. A distracting stimulus can also be added to increase attentional demands. Furthermore, by measuring premature responses in addition to accuracy, aspects of impulsivity can also be assessed in this task, although it has been suggested that impaired accuracy and impulsive responding can be related under some circumstances [282]. There are substantial strain differences in this task [282, 283]. Attention in this task is partially dependent on α5 nicotinic receptors in the prefrontal cortex

[284]. Nicotine improves attentional performance in the 5CSRTT [285], in particular increasing accuracy and decreasing omissions [286], but not under all conditions [287]. Chronic nicotine treatment appears to be necessary to see attentional improvements under at least some conditions [283]. Although Hoyle and colleagues [287] did not see effects of nicotine on attentional performance in wildtype mice in the 5CSRTT, these investigators observed that α7 nicotinic receptor knockout produced both attentional impairments and impulsivity in the 5CSRTT, confirming the findings of Young and colleagues [286] in this regard.

Limitations of the ways in which mouse models of human cognitive function parallel human cognitive processes, or cognitive dysfunction, would obviously limit the parallels that can be established between mouse studies and the contributions of these processes to nicotine cessation. With regard to cognitive dysfunctions induced by comorbid psychiatric disorders adequate modeling of the impact of the disorder on nicotine cessation would require combining both drug dependence and psychopathology models. As discussed above, there is evidence for nicotine-induced improvement in cognitive deficits associate with schizophrenia. Additionally, in schizophrenia patients some deficits that lead to self-treatment with nicotine may result from antipsychotic treatments rather than the disorder itself [35]. While there is little data from mice that identify clear interactions between nicotine and antipsychotics (including atypical antipsychotics), studies in rats suggest that validating such models in mice should be relatively straightforward [288]. As discussed above, effects of nicotine on antipsychotic-induced side effects does not explain all smoking in schizophrenia patients. However, modeling of both premorbid impairments and the exacerbation of those impairments by withdrawal will be essential for understanding smoking in schizophrenia. As the α7 nicotinic receptor may be especially involved in the cognitive effects of nicotine in schizophrenia patients, it is noteworthy to observe that similar differences in the α7 nicotinic receptor are also observed in a genetic mouse model (DBA/2 mice) of auditory gating deficits [289, 290], and nicotine improves these deficits [290]. Gene knockout of the α7 nicotinic receptor subunit itself produces a small impairment in spatial working memory in a water maze working memory task [291], while β2 nicotinic receptor knockout mice actually have improved spatial learning [292]. However, the nature of the improvements in spatial learning in β2 nicotinic receptor knockout mice was suggested to be the result of impairments in executive function in wild-type mice whereby these mice failed to alter their behavior in a variety of situations that required alternative behavioral strategies because of changes in the environment. A selective α7 nicotinic receptor agonist improved sensory gating in DBA/2 mice that show reduced basal function [252, 293]. Nicotine enhances prepulse inhibition in mice [294], but does so over a rather narrow dose range [295], as did varenicline in that study. α7 nicotinic receptor knockout mice have deficits in prepulse inhibition [255], consistent with a role for this receptor subunit in this type of sensory gating as well. In mice nicotine withdrawal impaired prepulse inhibition of startle in one study [296], as it did in humans [297], although another study in mice did not find prepulse inhibition deficits during nicotine withdrawal [298].

B3) Mouse models for differences in the rate of extinction of smoking-related conditioning

One of the complaints made by individuals addicted to nicotine, as an explanation for failure in nicotine cessation, is sensitivity to conditioned cues. One interpretation of such effects, whether they are mediated by cue-induced craving or habit mechanisms, is that stimuli previously associated with nicotine administration impede extinction. Indeed, there have been attempts to develop therapeutic extinction procedures, such as reduced nicotine cigarettes, and the effects of these extinction treatments have been assessed on brain activity associated with cue-induced craving [56]. Another possible explanation for the importance of these cues in nicotine cessation is not their establishment, but rather the effects of these cues during abstinence/extinction that influence reinstatement of drug-seeking behavior. Of course, there is a possibility that individuals may differ in rates of extinction of either classically or instrumentally conditioned behavior. Mouse procedures addressing such aspects of conditioning exist, although these methods have not been applied extensively to the study of nicotine. Nicotine may present additional complications in studies of extinction as withdrawal and conditioned cues may influence attentional and mnemonic processes, as discussed in the previous section.

Methods to study extinction and reinstatement of operant drug self-administration have been established. Mice will extinguish operant responding for nicotine and this response can be reinstated by stress [299]. Beyond this demonstration that these methods can be applied to mice, however, much remains to be done to elaborate the underlying biological and genetic basis of extinction and reinstatement of nicotine self-administration in mouse models. Similarly, both extinction and reinstatement of nicotine CPP have been demonstrated in mice [195]. However, with regard to extinction of conditioned cues, a variety of procedures have been used in extinction of CPP, which are of relevance for comparing possible therapeutic approaches to enhancing extinction during nicotine cessation. A most important question is whether the extinction is “active” or “passive”. In active extinction paradigms the conditioning procedure is repeated, but either the conditioned stimulus is presented in the absence of the unconditioned stimulus or the effect of the drug is blocked. In the case of CPP the subject is confined to the conditioned side of the apparatus, but either drug is not administered or the effect of the drug is blocked by an antagonist. In passive extinction the subject is exposed repeatedly to the apparatus without any drug administration and allowed to freely explore until drug-seeking behavior extinguishes (e.g. preference is lost). Preference in the CPP task can be reinstated either by administration of the drug, or by stress. In mice a passive procedure has been used with repeated trials at 24 hour intervals to extinguish CPP for nicotine, with a subsequent threshold dose of nicotine used to reinstate drug-seeking behavior, e.g. preference [195].

Given the effects of nicotine in learning and attentional procedures, particularly in aversively motivated tasks, and on stress, as discussed below, it is also important to consider the potential effects of nicotine on the extinction of aversively conditioned stimuli. Nicotine given during extinction of an aversively motivated task accelerated extinction, whether extinction occurred in the same context as training or not [300]. Nicotine had greater effects on between-session extinction than within-session extinction, suggesting that the effects were mediated by consolidation of extinction learning, although nicotine administration after

the tests did not enhance extinction. Interestingly, although nicotine had no effect on subsequent extinction when given during training, when nicotine was given during both training and extinction sessions, extinction was delayed, indicating that nicotine cues act in such a way as to increase persistence of the behavior. An important further consideration here, with regard to both the effects of nicotine on attention/memory and stress responses, is that withdrawal often produces effects that are opposite to the initial effects of nicotine. Therefore, if nicotine accelerates extinction, nicotine withdrawal may very well have the opposite effect, an important consideration for the potential role of extinction effects in nicotine cessation that has yet to be investigated.

B4) Mouse models for differences in subjective “craving” identified during and after acute nicotine withdrawal

Although the term “craving” refers to a subjective internal state, it has been modeled in animals based upon drug seeking under conditions that also occur in humans, in response to exposure to drug associated cues, stress and the drug itself. The reinstatement procedures discussed above are highly relevant to craving, based on the incorporation of these aspects of drug-seeking behavior. Although the mouse models discussed above certainly address several phenomena that are important aspects of craving phenomena, they also have certain weaknesses. In particular, the most commonly used method to address nicotine conditioning in mice, the CPP paradigm, addresses contextual conditioning – although this may depend greatly upon the way that the apparatus is constructed and, under some conditions, the conditioning may be primarily to discrete cues rather that contextual cues, mediated by the amygdala rather than the hippocampus (see [301]). Whether or not discrete stimuli involve hippocampal function depends on the procedure, as in the differences between delay cue conditioning and trace cue conditioning discussed above. Discrete cues are used in the reinstatement of operant self-administration, but this has not been examined in mice for nicotine, nor have other models that examine conditioning of discrete appetitive cues. The important consideration here is that, although contextual conditioning is certainly relevant to nicotine-induced conditioning and reinstatement in smokers, conditioning mediated by discrete cues, mediated by other brain structures such as the amygdala are very important as well, and these have not been extensively examined in mouse models.

B5) Mouse models for differences in possible “incubation” features that might enhance responsiveness to nicotine after a period of abstinence

A phenomenon termed “incubation” has been described in which subsequent drug seeking and cue-reactivity, in terms of reinstatement of operant drug self-administration, is amplified by a period of forced abstinence in rats [302]. The original description of this phenomenon was with cocaine, but it has also been demonstrated with nicotine [303]. This phenomenon would obviously be of potential relevance to nicotine addiction, particularly when individuals go through repeated quit attempts, periods of abstinence and reinstatement. Indeed, it has been reported recently that cue-induced craving shows “incubation”-like properties during abstinence [304]. The precise psychological process involved here is unknown, and indeed it has been suggested that the key process may be suppression of responses to cues early in withdrawal [305], but may also involve reconsolidation of memories of drug-associated cues [306]. As with regard to the discussion in the previous

section, the nature of those cues must be carefully considered. In many protocols for reinstatement, incubation and reconsolidation the critical cues involve cue conditioning mediated by the amygdala. Incubation has also been described for conditioned aversive responses as well [307] and is thought to model some aspects of post-traumatic stress disorder. The incubation procedure has been applied to spontaneous and cue-induced reinstatement of operant responding for cocaine in mice [308], but not yet for nicotine.

C: Mouse models for differences in “physiologic”, non-mnemonic withdrawal signs, such as weight gain

Consistent with human observations, weight reduction is observed with repeated nicotine treatments in mice [309]. In further exploration of the genetic basis of such effects it will be important to separately address the difference between nicotine effects on premorbid obesity, from those effects produced by chronic nicotine administration and withdrawal. In such models, it will be advantageous to monitor a number of physiological and behavioral parameters that might lead to nicotine self-treatment, for which tolerance develops at different rates [143]. Nicotine administration can regulate both food intake and energy expenditure. Thus, Hur and colleagues [310] have recently reported weight loss in mice treated daily with nicotine for two weeks. Interestingly, weight gain during nicotine withdrawal was almost entirely due to decreased energy expenditure rather than changes in caloric intake. Another issue for such studies will be the mechanism of nicotine administration, voluntary administration obviously modeling the human condition the best. By gradually increasing the nicotine concentration (up to 500 μg/mL) high levels of consumption (>60 mg/kg/day) and blood levels of nicotine (>50 ng/ml) can be attained in mice [187]. Under these conditions reduced weight gain is observed, similar to human smokers.

D: Mouse models for differences in the degree to which smoking is driven by stress relief and the degree to which stress exacerbates craving and relapse

As discussed above, smokers consistently indicate that nicotine is “stress” reducing, that stress is exacerbated by nicotine withdrawal, and that these factors contribute to the likelihood of relapse. There is also clinical evidence to support this view. However, despite these common reports from smokers there is not very much evidence that nicotine induces stress-relief or has anxiolytic effects in animal models. Perhaps, this is because the anxiolytic effects of nicotine in mice, like many of its other effects, occur over a very narrow range, at low doses [155, 311, 312], with higher doses being anxiogenic [311, 312]. Under some circumstances only anxiogenic effects are observed, but those effects are very short-lasting [313]. These anxiogenic effects of nicotine are dependent on norepinephrine systems [313], in contrast to many of the other effects of nicotine, which would likely suggest that there would be a different neurobiological and genetic basis for these effects of nicotine.

More specific nicotinic agonists can be anxiolytic [252, 262]. If nicotine produces a combination of anxiolytic and anxiogenic effects it seems likely that more specific agonists might have a broader range of anxiolytic effects than nicotine. Additionally, the anxiolytic effects of nicotine may only be apparent under certain conditions. For example, although

nicotine by itself did not have anxiolytic effects in one study, it did reverse the anxiogenic effects of caffeine [314]. Interestingly, Adriani et al. [155] also showed differential effects of nicotine on anxiety in adolescent and adult mice. The anxiogenic effects may be at least partially mediated by β3 and β4 nicotinic-containing receptors as β3 and β4 knockout mice show reduced anxiety in some tests [315, 316]. Interestingly, gene knockout of the α7 nicotinic receptor subunit has no effect in tests of anxiety [132], which is in contrast to its effects on learning [184]. The effects of nicotine may also be more stress-relieving than anxiolytic. Nicotine has been found to block stress-induced hyperthermia [317], although the nature of this effect is questionable given that nicotine can decrease temperature by itself [129].

It may be possible that nicotine effects on stress or anxiety may emerge only after chronic nicotine treatment or chronic stress exposure. Anxiety levels in naïve mice do not predict subsequent oral nicotine consumption [318]. Nicotine withdrawal after chronic treatment increases anxiety in the elevated plus maze [309, 319], and there is variation in this response. Although basal anxiety does not predict subsequent voluntary nicotine consumption [318], anxiety levels early during withdrawal after a period of forced oral nicotine consumption does predict subsequent voluntary oral nicotine consumption [319]. Chronic nicotine also reverses deficits in spontaneous alternation and anhedonia produced by a chronic mild stress regimen [273]. Chronic stress increases the expression of α7 nicotinic receptor mRNA in the hippocampus [320]. When mice were tested two hours after a chronic nicotine regimen they exhibited a depression-like profile, similar to a chronic stress regimen, in the forced swim test and tail suspension test [321]. Nonetheless, the chronic nicotine treatment reversed the anhedonia produced by chronic stress.

Although mice that were selected for differential stress levels did not differ in the acquisition, extinction or level of nicotine self-administration, high-stress mice readily reinstated after a stressor, whereas low-stress mice did not [299], which could be interpreted to be consistent with self-medication to ameliorate stress, and might be directly related to certain essential features of nicotine addiction. Furthermore, mice that over-express the R isoform of acetylcholinesterase have increased anxiety in the elevated plus maze, and this anxiety is normalized by chronic forced nicotine consumption [322]. The effects of nicotine on stress mechanisms, or the influence of stressors on nicotine effects, may also be sex dependent. Female mice, but not male mice, were more anxious in the elevated plus maze after chronic nicotine consumption [323]. Note that this test was not done during withdrawal, but rather while still consuming nicotine, indicating that chronic nicotine may increase anxiety creating a potential positive feedback loop that leads to further, and perhaps accelerated, nicotine consumption, provided that acute nicotine consumption is still anxiolytic.

In applying these tests to transgenic mice, background strain will be an important consideration as there are substantial differences in both acute and chronic nicotine responses among mouse strains. Strain does not just affect sensitivity (i.e., dose-response function) to nicotine, but in some cases whether particular effects are observed at all: acute nicotine has pronounced anxiolytic effects in C57BL/6J mice, but anxiogenic effects in DBA/2 mice; nicotine produces CPP in C57BL/6J mice but not DBA/2 mice; and although

signs of somatic withdrawal are more pronounced in DBA/2 mice, these mice demonstrate no signs of affective withdrawal based on mecamylamine-induced CPA [199].

E: Mouse models of differences in affective (or other comorbid) symptoms, either prior to nicotine exposure or those emerging during withdrawal

Differences in premorbid affective state, as well as changes in affective state upon nicotine withdrawal may both contribute to smoking. Stress paradigms are commonly used to induce "depressive-like" states. Thus, chronic stress paradigms can induce anhedonia, and these effects can be reversed by nicotine treatment [273]. Furthermore, it also appears to be the case that chronic nicotine treatment, and subsequent withdrawal, produces effects similar to chronic stress regimens, including a depression-like profile: deficits in the forced swim and tail suspension tests [321], and elevations in ICSS thresholds [124, 137]. The observation that chronic nicotine treatment reversed the anhedonia produced by chronic stress suggests that some individuals persist at smoking, or fail at nicotine cessation, because of withdrawal-induced dysphoria, which might have contributed to nicotine self-administration after a chronic stress procedure in mice [299].

Other approaches that can be taken to assess affective differences, either premorbid differences or those that occur during withdrawal, include measurement of oral-facial responses to palatable (sucrose) and unpalatable substances (quinine). However, neither chronic nicotine administration, nor withdrawal, alters affective state using these behavioral outcomes [324]. As mentioned in previous sections, chronic nicotine administration produced elevations in brain stimulation reward thresholds (anhedonia) as well as increased anxiety upon either spontaneous or precipitated nicotine withdrawal in C57BL/6J and BALB/cByJ mice [124, 137]. Furthermore, antagonist-precipitated withdrawal produces an aversive affective state as can be demonstrated using a conditioned place avoidance procedure [325].

F: Mouse models of individual differences in delayed discounting

Delayed-discounting procedures have been used in mice and involve operant procedures that are well-established in mice, but in paradigms in which alternative responses result in reinforcement that differs in both magnitude and the delay until the reinforcer is received [326]. Importantly, that study showed that in mice, as in humans, there are differences in delayed discounting between adolescent and adult subjects, although the difference was strain dependent. This use of this procedure opens the way to genetic studies of the basis of delayed discounting in mice that might be applicable to nicotine cessation studies.

Summary: What paradigms in mice are necessary to create a battery to investigate the specific contributions of individual genetic differences to nicotine cessation?—In part because of the multiple behavioral effects of nicotine, and the multiple behavioral effects of nicotine withdrawal that may contribute to differences in ability to abstain from nicotine, multiple behavioral tests will be necessary to produce a complete analysis of genetic contributions to nicotine cessation in mouse models. Indeed, if each of the genetic contributions to cessation that are identified in human genetic studies is relatively specific, it then raises the possibility of false negatives if a complete analysis of

the potential contributions to nicotine cessation is not undertaken when hypotheses about the role of these genes in nicotine cessation are examined in mouse models. This analysis suggests a certain view of the genetics of addiction, and in particular nicotine cessation, in which the genetic basis is both the result of additive effects of many genes and for which there is substantial genetic heterogeneity among individuals. This assertion is supported by the results of numerous recent GWAS studies, and the gene structure suggested by these studies must be taken into account as mouse studies are conducted to elaborate the specific roles of these genes in nicotine addiction and nicotine cessation.

Table 1 summarizes the traits associated with nicotine cessation in humans for which there is strong human genetic data (at least in most cases, the exceptions being newly described phenomena, such as incubation), that should be included in a comprehensive approach to the study of the genetics of nicotine cessation; these features include the strength of dependence, differences in the strength or rate of learning (including both conditioning and habit formation), the extent of withdrawal deficits on memory or cognition, differences in the rate of extinction, differences in craving, differences in the extent of non-cognitive withdrawal symptoms, the degree to which nicotine is used to alleviate stress or anxiety, the degree to which withdrawal is associated with affective symptoms, and impaired delay discounting. These phenomena can be categorized in three ways, as premorbid impairments that facilitate the addictive process, as premorbid impairments that lead to self-treatment because of the acute effects of nicotine, and symptoms that develop in withdrawal (or after chronic use) that lead to self-treatment. This last aspect of nicotine cessation, in particular, has not been modeled extensively in mice, although it is often been suggested to contribute to failure in nicotine cessation attempts. Specific mouse models which address each of these human phenotypes, and can be used to evaluate specific genetic contributions to these phenotypes, are summarized in Table 2. Although this review has attempted to provide a comprehensive analysis of the human features that should be modeled, and corresponding mouse models, this should be considered to be a first approximation of such a comprehensive battery that will be influenced by ongoing studies as these specific features are examined in more detail in humans and as more comprehensive studies of mouse genetic models are conducted.

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Table 1

Addiction characteristics/processes for which there is evidence of a strong genetic basis in humans

Table 2

Animal models of human addiction characteristics/processes for which there is evidence of a strong genetic basis

Addiction Characteristic/Process	Page	Model (s)
Strength of Dependence	16	IV Self-administration including concurrent punishment schedule, progressive ratio, extinction and reinstatement
		Oral self-administration with assessment of withdrawal
Cognition:		
Conditioning/Habit Mechanisms	26	Conditioned Place Preference
		Withdrawal-induced Place Avoidance
		Cue-induced reinstatement
		Habit: Reinforcer devaluation after over-learning
Withdrawal Deficits in Memory/Cognition	32	Delay cue/contextual conditioning - baseline and nicotine withdrawal
		5-choice serial reaction time task- baseline and nicotine withdrawal
		Schizophrenia model of impaired prepulse inhibition of startle
Rate of Extinction	40	Extinction of Conditioned Place Preference
		IV Self-administration extinction; extinction of cue-induced reinstatement
Craving	42	Cue, drug and stress-induced reinstatement of CPP
		Cue, drug and stress-induced reinstatement of self-administration
Incubation	43	Self-administration incubation procedure
Non-cognitive withdrawal symptoms	44	Chronic Nicotine/Withdrawal regulation of weight and food intake
Stress relief	45	Extent to which nicotine self-administration (oral or iv) is increased in response to acute or repeated stressors
Affective symptoms in withdrawal	48	Effect of withdrawal in standard depression/anxiety models, including assessment of anhedonia by ICSS or sucrose preference procedures
Impaired delayed discounting	49	Delayed discounting for food/nicotine reinforcement