

# Nicotine-Dependence Endophenotypes in Chronic Smokers

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*A key area in understanding the biology of smoking behavior is the search for measures of smoking persistence, which, in turn, may help predict the likelihood of successful cessation among long-term users of tobacco. This chapter explores the existing evidence base for purported endophenotypes for nicotine dependence in chronic smokers and discusses measures in the following key areas:*

- *Motivational measures, including reinforcement, as measured by self-administration of nicotine, and reward (i.e., the subjective evaluation of the hedonic effects of smoking)*
- *Sensory measures, including resting electroencephalogram (EEG) activity, event-related potentials (ERPs), and the prepulse inhibition (PPI) of startle response*
- *Measures of cognitive function, including attention and vigilance as well as working memory*
- *Measures of abstinence-induced and cue-induced craving*
- *Affective regulation and impulse control*

*Each of these measures is examined from a standpoint of biological plausibility, objective measurement criteria, genetic influences, and association with nicotine dependence. Available research shows a relationship between motivational measures and dependence, as well as evidence of heritability and genetic associations for many sensory, cognitive, affective, and behavioral measures. Further research is indicated to establish the potential viability of measures such as these as endophenotypes for nicotine dependence.*

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## Introduction

This chapter examines purported endophenotypes relevant to smoking persistence—that is, phenotypes that can be measured objectively in chronic smokers and that predict continued smoking versus cessation. Nicotine dependence requires chronic nicotine exposure, which produces neuroadaptive changes that promote continued smoking. First, a brief overview is provided of the evidence for specific genetic influences on nicotine dependence, a prerequisite in the search for valid endophenotypes. Then, two overarching areas of potential endophenotypes are covered: (1) measures of smoking’s “motivational effects” that directly reflect smoking persistence: smoking reinforcement (i.e., self-administration) and reward; and (2) measures of smoking’s other effects, and of responses to abstinence, on sensory processing, cognitive, affective, and behavioral (especially impulsivity) functions that may help explain smoking’s motivational influences. This latter section includes acute craving, or urge to smoke, because craving measures encompass each of these response dimensions. Also discussed are the potential endophenotype measures of smoking (and nicotine) effects in nondeprived smokers, abstinence-induced effects in nicotine-deprived smokers, and smoking’s reversal of these abstinence effects. As noted in chapter 8, endophenotypes can be conceptualized as one of three “subtypes”: (1) component phenotype, (2) intermediate phenotype, and (3) covariate.<sup>1</sup> While chapter 8 focused on intermediate phenotypes, or mechanisms believed to be part of the causal chain in the disorder, this chapter will emphasize component phenotypes, which capture one aspect of the multidimensional disorder phenotype but are not necessarily part of the causal chain. The focus here differs from that of the previous chapter; the population of interest in this chapter comprises those already dependent on nicotine (i.e., already “affected”). Therefore,

the potential endophenotypes to be discussed will be responses to nicotine or smoking, and other measures, that are believed to reflect the critical dimensions of the nicotine-dependence phenotype.

It is assumed that the motivational effects of smoking, the first area, are more proximal to persistence of smoking behavior, or dependence, virtually by definition, as they are usually indexed by measures capturing smoking- or nicotine-seeking behavior or its direct hedonic effects (reward). It is also assumed that the other effects of smoking and abstinence, the second area, are more distal to smoking persistence, again virtually by definition, as they are not indexed by measures of smoking-seeking behavior or direct hedonic effects but rather by responses on other dimensions that may or may not relate to smoking behavior. Thus, endophenotypes related to dependence may be identified as proximal or distal to smoking persistence. While this organization does not assume one area is more important than the other, it does presume that all factors promoting dependence in chronic smokers act by increasing smoking’s motivational effects. Consequently, this view also assumes a general pathway to smoking persistence; that is, various acute effects of smoking and abstinence serve to foster greater smoking reinforcement and reward, directly promoting smoking persistence (dependence).

For the first area, drug-motivated behavior is the centerpiece of any drug dependence. The existing criteria for diagnosing drug dependence in psychiatry emphasize persistence of drug use (i.e., self-administration) despite adverse consequences for the user.<sup>2</sup> Meeting all criteria that reflect persistence of smoking behavior is sufficient for a diagnosis of dependence, while meeting all criteria other than those reflecting persistence of smoking (namely, withdrawal) would not. Identification of potential endophenotypes

reflecting reinforcement may be relatively straightforward, as reinforcement is usually indexed by drug self-administration, a discrete behavior that can be measured acutely in the laboratory. Thus, individual differences in smoking or nicotine reinforcement in chronic smokers can be assessed objectively in a number of ways. These include measures of cigarette consumption or brief laboratory evaluations of self-administration of nicotine administered by novel means (e.g., gum, nasal spray). Within the area of motivational mechanisms, smoking or nicotine's "rewarding" (or hedonic) effects are included; these are direct evaluations of the smoking experience that may help explain reinforcement. Identification of endophenotypes of smoking reward may be more complicated because reward in humans is typically measured with self-report questionnaires. However, basic research with nonhuman animals suggests the possibility of more objective measures that reflect drug reward. This research will be discussed in terms of its potential applicability to identifying endophenotypes of smoking or nicotine reward in humans.

For the second broad area—that is, nicotine or abstinence effects—acute and chronic nicotine exposure produces physiological, cognitive, affective, and behavioral responses in both animals and humans. Chronic exposure, the focus of this chapter, can lead to deficits in these functions following smoking abstinence, reflecting the onset of withdrawal. Nicotine delivered acutely, via smoking or other delivery systems, may enhance function and often reverses abstinence-induced deficits. These effects of nicotine may, in turn, prompt smoking or nicotine-seeking behavior to enhance function and/or to ameliorate withdrawal symptoms. Thus, nicotine or abstinence effects can help explain smoking's motivational effects. Craving is included in this section because it purportedly contains elements of each response domain

covered here, including physiological, cognitive, affective, and behavioral aspects. Note that craving is separated here into two types: abstinence induced and cue induced. Although craving, especially abstinence induced, is typically measured via self-report, it may also be captured by objective measures being explored in human studies of cue-induced craving. In terms of endophenotype measures, relatively few of the objective measures of deficits or enhancements due to nicotine have been clearly related to dependence. This chapter will review existing measures, identify gaps in knowledge related to the viability of these measures as endophenotypes, and discuss future directions for identifying and validating nicotine-dependence endophenotypes in chronic smokers.

Finally, several formal self-report dependence measures have been developed to capture putative dimensions of dependence, and some have been related to ability to quit smoking, or smoking persistence, with varying predictive validity. These measures, such as the Fagerström Test for Nicotine Dependence (FTND),<sup>3</sup> the Wisconsin Inventory of Smoking Dependence Motives,<sup>4</sup> and the Nicotine Dependence Syndrome Scale,<sup>5</sup> generally assess smoking patterns, smoking effects, and the consequences of abstinence as part of clinical research aimed at predicting quitting success. Such responses could reflect facets of the measures of interest here, specifically smoking persistence and reinforcement or reward (i.e., motivational effects), as well as effects experienced during smoking abstinence and sensitivity to acute nicotine effects on various responses (i.e., nicotine or abstinence effects). However, these self-report dependence measures will not be examined in this chapter. Instead, the goal of this chapter is to identify objective laboratory procedures that may reliably capture facets of smoking reinforcement or reward, effects of abstinence, and acute responses to smoking that relate to dependence. The description

### Smoking Persistence Versus Smoking Onset: An Area for Endophenotype Research

Many of the processes involved in the onset of smoking are likely to be different from those involved in smoking persistence. Chapter 8 explores potential phenotypes and endophenotypes for nicotine dependence at or before nicotine exposure. The areas investigated include some measures similar to those in this chapter, such as nicotine reinforcement (self-administration) and reward, as well as other potential endophenotype areas such as latency and age of onset. This chapter focuses on purported endophenotypes relevant to smoking persistence—that is, phenotypes that can be measured objectively in chronic smokers and that predict continued smoking versus cessation, with inability to quit being the primary index of dependence in chronic smokers. These, in turn, have the potential to help understand the biology of tobacco use among a population at greatest risk for tobacco-related health problems.

of these self-report dependence measures and their relationship to dependence are comprehensively discussed in chapter 3 and described elsewhere.<sup>5</sup>

## Rationale for Investigating Endophenotypes of Chronic Nicotine Exposure

### Genetic Influences on Nicotine Dependence

Nicotine dependence, which underlies persistent smoking, is a complex trait, influenced by genetic and environmental factors. Twin studies indicate that approximately 60%–70% of the variance in nicotine dependence and smoking persistence is due to genetic influences.<sup>6,7</sup> Further, at least 50% of the variance in successful quitting, given a quit attempt, is due to heritable factors.<sup>8</sup> Nicotine dependence has a strong genetic association with alcohol dependence,<sup>9</sup> and linkage studies have pointed to loci common to alcohol and nicotine-dependence susceptibility.<sup>10</sup> Common genetic influences are also thought to contribute to nicotine

dependence, personality traits, and psychiatric conditions, such as attention deficit hyperactivity disorder (ADHD),<sup>11</sup> depression,<sup>12</sup> and schizophrenia;<sup>13</sup> however, interactions of biological and environmental factors clearly play a role.<sup>14</sup>

Given consistent evidence for the heritability of nicotine dependence, attention has shifted to investigations of specific genetic influences. Genetic variation in enzymes (e.g., *CYP2A6*) that metabolize nicotine to its inactive forms (cotinine and 3-hydroxycotinine) influence peripheral levels of nicotine and smoking behaviors.<sup>15</sup> Smokers who are genetically faster metabolizers of nicotine smoke more cigarettes per day, are more dependent on nicotine, and are more likely to relapse following transdermal nicotine replacement therapy (NRT) than are smokers who are slower metabolizers (e.g., carriers of \*2, \*4, \*9A, and \*12A alleles).<sup>16,17</sup> Thus, measures of nicotine metabolism are important endophenotype measures.

Candidate genes in neurobiological pathways mediating drug reward have been extensively studied for associations with nicotine dependence. Nicotine binds to neuronal nicotinic acetylcholine receptors (nAChRs) expressed on dopamine and  $\gamma$ -aminobutyric acid (GABA) neurons in the ventral tegmental area (VTA), resulting in

increased dopamine release in the nucleus accumbens.<sup>14,18</sup> Despite the importance of nAChRs in nicotine dependence, particularly the  $\alpha 4\beta 2$  subtypes,<sup>19</sup> data on the functional relevance of genetic polymorphisms are limited, with the possible exception of data on two functional variants in *CHRNA4*.<sup>20</sup>

A few SNPs in *CHRNA4* have been examined for associations with nicotine dependence, but findings were not significant.<sup>21</sup> However, a more comprehensive analysis of *CHRNA4* suggests that variation in *CHRNA4* is associated with smoking cessation.<sup>22</sup>

In addition, there is growing evidence for association of *CHRNA4* haplotypes with nicotine dependence.<sup>23,24</sup> Other work shows that haplotypes at the *CHRNA5-A3-B4* locus are associated with nicotine-dependence severity as indexed by the FTND among smokers who began smoking daily by 16 years of age, but not among those who began smoking after 16 years of age.<sup>25</sup> The age dependence of these findings highlight the notion, discussed in chapters 5–8, that influences on dependence susceptibility, including genetics, can vary by age.

Given the central role of dopamine signaling in the reinforcing and rewarding effects of nicotine, alcohol, and other addictive drugs,<sup>26–28</sup> many initial studies focused on the common *\*TAQIA* polymorphism in a neighboring gene, *ANKKI*.<sup>29</sup> With respect to smoking behavior, some association studies have reported a higher prevalence of the low-activity *DRD2\*TAQI AI* allele among smokers compared to nonsmokers,<sup>30,31</sup> while other findings have been negative.<sup>32</sup> Mixed results have also been reported for associations of a variable number tandem repeat (VNTR) polymorphism in the 3' end of the dopamine transporter (*SLC6A3*) gene with smoking behavior.<sup>33–35</sup>

More robust findings have been observed for polymorphisms in *DRD2* with documented functional effects—for example, variants that alter transcription or translation. For instance, the promoter variant

*DRD2-141C INS/DEL*, associated with transcriptional efficiency, has been associated with response to pharmacotherapy for smoking cessation.<sup>36</sup> The reduced activity *\*7-repeat* allele of the *DRD4* gene VNTR has been associated with smoking persistence.<sup>37,38</sup> The high-activity (*\*VAL*) allele of the *COMT* gene, associated with more rapid degradation of dopamine, has been associated with smoking persistence in a retrospective case-control study and in a prospective smoking cessation study.<sup>39</sup>

Nicotine also increases levels of endogenous opioids that bind to mu opioid receptors on GABA interneurons in the VTA.<sup>28</sup> Consistent with neurobiological evidence, the mu opioid receptor (*OPRM1*) *ASN40ASP* functional variant has been associated with response to NRT; however, the direction of association in different populations has not been consistent.<sup>40,41</sup> A study comparing smokers with high versus low levels of nicotine dependence did not find associations with this *OPRM1* variant; however, haplotype analysis suggests that other variants, which may be in linkage disequilibrium with the *ASN40ASP* polymorphism, are linked with this smoking phenotype.<sup>42</sup> Finally, despite effects of nicotine on serotonin neurotransmission, there is no strong evidence linking smoking behavior or smoking cessation with genes in the serotonin pathway.<sup>43,44</sup> Thus, it has proven difficult to identify candidate genes with robust, replicable associations with nicotine dependence and smoking persistence.

In addition to the candidate gene approach used in the studies above, specific genetic influences on nicotine dependence are being identified through linkage analysis and genome-wide association studies.<sup>45–48</sup> Similar analyses have been performed to predict successful smoking cessation.<sup>49</sup> In contrast to the hypothesis-driven approach based on neurobiology described above, genome-wide studies have the potential to identify novel susceptibility loci that may not be

considered as *a priori* candidate genes. As with the candidate gene studies, findings from these approaches require independent validation. In addition, pharmacological challenge studies (e.g., dopamine depletion, agonist or antagonist compounds) may help to elucidate novel neurobiological pathways that influence endophenotypes of relevance to nicotine dependence.

## The Case for Endophenotypes

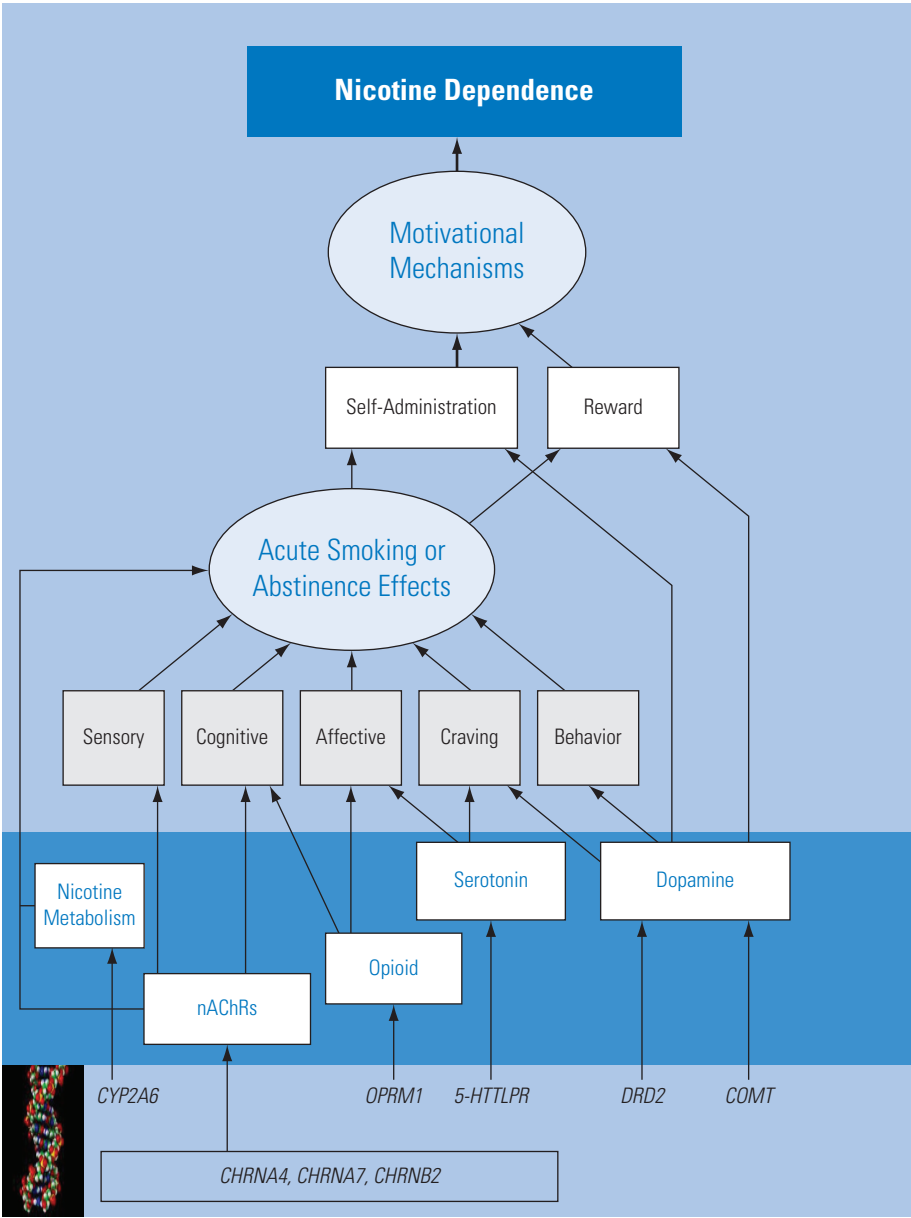
As described in the introduction to chapter 8, one promising approach to elucidate the genetic basis of nicotine dependence is to study the underlying motivational, affective, and neurocognitive processes that underlie this complex phenotype.<sup>50,51</sup> These intermediate measures of nicotine dependence, referred to as “endophenotypes,” are thought to be more proximal biologically to their genetic antecedents than are the complex behavioral phenotypes described above and, therefore, may provide a stronger genetic signal;<sup>51</sup> however, this point is the subject of some debate.<sup>52</sup> In the context of nicotine dependence, the optimal endophenotype measures would have a biologically plausible link to nicotine dependence and would be reliable, heritable, and valid (i.e., predictive of nicotine dependence, such as predicting smoking persistence versus abstinence after a quit attempt). Although many candidate endophenotype measures have *potential* utility in genetic studies of nicotine dependence, few meet all of these criteria.

Figure 9.1 illustrates the potential links between genes, neurochemical processes, and behavioral and physiological responses. Selected examples of genes coding for proteins involved in the biosynthesis, transport (e.g., *5-HTTLPR*), and metabolism (e.g., *COMT*) of neurotransmitters (e.g., serotonin, dopamine), and those coding for receptors (e.g., *DRD2*, *OPRM1*) are depicted in the shaded area. Also illustrated

are genes that code for nicotine-metabolizing enzymes (e.g., *CYP2A6*) and nAChRs that have been implicated in nicotine dependence (e.g., *CHRNA4*, *CHRNA7*, *CHRNA2*). These neurochemical processes, in turn, influence the specific nicotine effects (e.g., effects on affect and cognition) or abstinence effects in chronic smokers that help explain smoking’s motivational effects. These processes may also directly affect those motivational effects. Measures of smoking’s various motivational effects (first area) and nicotine or abstinence effects (second area) are viewed here as potential endophenotypes of dependence. They differ primarily in their proximity to dependence, with the motivational effects more proximal, and nicotine or abstinence effects less proximal, to dependence.

In the sections below, evidence is described regarding the potential utility of different endophenotype measures associated with chronic exposure to nicotine and reflecting either of the two broad areas: smoking’s motivational effects or the acute effects of nicotine or abstinence that may promote those motivational effects. For each endophenotype construct, evidence is reviewed pertinent to the previously noted four criteria in the evaluation of the utility of each as endophenotypes: (1) biological plausibility—that is clinical evidence (typically involving self-report) linking a response area to dependence, as well as the neurobiological basis for specific nicotine effects, including findings from animal models, and preclinical evidence suggesting genetic influences on those effects; (2) reliability—standardized, objective measurement of the construct in humans; (3) heritability—evidence for genetic influences in humans from heritability, linkage, and candidate gene studies; and (4) predictive validity—evidence supporting a relationship of the measure to nicotine dependence in chronic smokers (i.e., smoking persistence). As will become readily apparent, evidence for the association of most endophenotype measures to nicotine

**Figure 9.1** Example of How Potential Endophenotypes Can Link Genes to Nicotine-Dependence Risk



*Note.* Endophenotype areas are presented in gray squares, divided into motivational mechanisms and acute smoking or abstinence effects, the two broad areas outlined in the chapter. Selected examples of genes (bottom row) that contribute to neurotransmitter activity and receptor function (dark blue bar) related to these endophenotype areas can be identified. This figure is illustrative only and does not reflect a consensus on the factors responsible for neurotransmitter function or for the endophenotype areas.



dependence, the fourth criterion, is limited. Therefore, studies are included that are suggestive of an association, such as those documenting differences between smokers and nonsmokers, in addition to studies relating the endophenotype to validated dependence measures and to abstinence outcomes. For each endophenotype measure, the limitations as well as gaps in knowledge that may be addressed in future research are discussed. Also, since most research has focused on cigarette smoking, rather than on other forms of tobacco use, the focus will be on this aspect of nicotine dependence.

## Motivational Mechanisms

### Reinforcement

The concept of drug reinforcement is defined by the degree to which the drug is self-administered, or in other words, the degree to which it increases the probability of a behavior that leads to administration of that drug (such as pressing a lever or inhaling on a lit cigarette).<sup>53</sup> Such behavior is readily assessed in animal models, as well as in humans.

### Biological Plausibility

#### Preclinical Research

Although diverse factors influence drug reinforcement, one common factor across all drugs of abuse is that they activate the mesolimbic dopaminergic system.<sup>54–56</sup> Dopaminergic neurons in the VTA of the midbrain send efferent projections to areas involved in drug-motivated behavior (and reward) such as the nucleus accumbens, amygdala, and the prefrontal cortex.<sup>57–59</sup> Nicotine stimulates the release of dopamine in the nucleus accumbens via effects at nAChRs in the VTA.<sup>60–63</sup> However, it is not only activation of the nucleus

accumbens that mediates reinforcement but also the pattern of activation. Drug-related stimuli shift the firing of dopamine neurons from tonic or single-spike activity to a phasic pattern of activation.<sup>64</sup> Nicotine, via desensitization of  $\alpha 4 \beta 2$  nAChRs, shifts dopamine release in the nucleus accumbens to a phasic pattern of release.<sup>65,66</sup> Thus, the reinforcing properties of nicotine may be related to the ability of nicotine to increase the phasic pattern of VTA activation and dopamine release.

Two routes of administration commonly used in animal research to assess the reinforcing effects of nicotine are intravenous (IV) nicotine self-administration and oral nicotine self-administration. The behavioral and pharmacological features of each approach are briefly reviewed next, with an emphasis on genetic analyses of reinforcement findings in preclinical models.

#### Intravenous Self-Administration

Multiple studies have demonstrated that rodents will self-administer IV nicotine.<sup>67–76</sup> The most common procedure, developed by Corrigall and Coen,<sup>68</sup> was adapted from earlier methods of self-administration of other drugs in rodent models. In this IV self-administration procedure, rodents are presented with two levers in a test apparatus. Animals in the experimental group access an active lever, which results in jugular vein administration of nicotine, and an “inactive” lever that has no programmed consequences. The inactive lever is a control condition used to determine whether study procedures nonspecifically increase behavior (i.e., increase both active and inactive lever pressing via changes in general locomotor behavior) or specifically increase nicotine reinforcement behavior (i.e., active lever pressing only). For animals in the control group, the active lever delivers saline, while the inactive lever has no consequences; as expected, control animals emit low



levels of pressing on either lever. The rate of lever pressing is then compared between groups; a higher rate of pressing the active lever that delivers nicotine indicates that nicotine is reinforcing lever pressing.<sup>68,69,77</sup> Importantly, responding for nicotine can be greatly enhanced by the stimuli associated with nicotine infusions, such that these stimuli (commonly called “cues”) become secondary reinforcers and able to support (i.e., reinforce) responding independent of nicotine availability.<sup>78</sup> Examples of such cues include tones and brief onset or offset of animal chamber lights. Other variations on this self-administration procedure have been used, such as by varying the particular behavior contingent on drug administration (e.g., a nose-poke response instead of lever pressing), but the basic study designs are essentially the same.

Evidence suggests that the reinforcing properties of IV nicotine self-administration result from nicotine-mediated activation of the mesolimbic dopamine system. First, rats will self-administer nicotine into the posterior VTA;<sup>79</sup> this demonstrates that nicotine effects in the VTA are sufficient to support nicotine self-administration. Second, disruption of dopaminergic processes in the VTA decreases IV nicotine self-administration. For example, the D1 antagonist SCH23390 and the D2 antagonist spiperone both decrease nicotine self-administration.<sup>80</sup> Furthermore, 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens reduce dopamine levels in the nucleus accumbens by 92.9% and disrupt IV nicotine self-administration.<sup>81</sup>

Many different nAChRs exist in the human,<sup>19</sup> but only a few appear to be potentially important for understanding nicotine dependence. In particular, the  $\alpha 4\beta 2$  nAChRs are thought to mediate the reinforcing properties of nicotine. Dihydro-beta-erythroidine (DH $\beta$ E), an nAChR antagonist with high affinity for the  $\alpha 4\beta 2$  nAChRs, decreases nicotine self-administration,<sup>82</sup>

and direct VTA infusion of DH $\beta$ E decreases IV nicotine self-administration.<sup>83</sup> Self-administration of nicotine, but not cocaine (showing selectivity), is decreased in  $\beta 2$  knockout mice compared to wild-type mice.<sup>84,85</sup> These studies not only suggest the involvement of VTA dopamine processes in nicotine dependence but also suggest involvement of the  $\alpha 4\beta 2$  nAChRs.

Comparison of IV nicotine self-administration across strains of rats suggests that natural genetic variance may influence IV nicotine self-administration. In a study comparing choice of IV nicotine self-administration across Sprague-Dawley rats, Long-Evans rats, Fischer 344 (F344) rats, and Lewis rats that were either preexposed to nicotine or saline for seven days before self-administration, Sprague-Dawley rats showed high levels of IV nicotine self-administration for all three doses tested (0.015, 0.03, and 0.06 milligrams per kilogram [mg/kg]/infusion) regardless of preexposure condition.<sup>86</sup> Long-Evans rats also self-administered nicotine; however, this was limited to rats in the saline preexposure condition and to higher doses of nicotine. Neither F344 nor Lewis rats reliably self-administered nicotine. Clearly, genetic differences in nicotine self-administration (and thus, reinforcement) exist.

Rats selectively bred for high versus low alcohol preference demonstrate a genetic influence on nicotine self-administration as well, suggesting a common genetic influence. Alcohol-preferring rats have twice the intake of IV nicotine as nonpreferring rats.<sup>87</sup> Mice bred for increased sensitivity for the sedative effects of alcohol are more sensitive to the effects of nicotine on thermoregulation and locomotor activity.<sup>88,89</sup> In addition, mice bred for high sensitivity to the sedative effects of alcohol develop greater tolerance to nicotine than do mice bred for low sensitivity.<sup>90</sup> These findings in rodent models are consistent with the notion of individual differences

in vulnerability to comorbid alcohol and nicotine dependence in humans.<sup>91</sup>

### Oral Self-Administration

In addition to IV self-administration, rodents will also self-administer nicotine orally.<sup>92–96</sup> IV administration, used in rat models, is difficult to achieve with mice for a variety of practical reasons. Thus, oral self-administration is the common method for studying drug reinforcement in mice, although it is also used with rats. As a result, differences in results between IV and oral methods may often be due to species differences, although the kinetics of nicotine intake between these methods (rapid with IV, slow with oral) can also account for different results.<sup>97</sup>

Multiple methods have been used successfully for oral self-administration. One is a 24-hour, free-access approach in which animals are individually housed in cages with two bottles—one bottle containing water and the other nicotine—and consumption is compared between bottles.<sup>93</sup> The restricted access method is a variant of the two-bottle-choice method. Animals are maintained on water restriction except for a given period (e.g., 2 hours/day) during which they have access to two tubes, one filled with water and the other filled with a nicotine solution.<sup>92</sup> Another approach is to use an operant oral self-administration procedure; animals are water restricted except in the operant trials during which a response on one lever delivers a nicotine solution and a response on the other lever delivers water.<sup>94</sup> Finally, some studies have combined a sucrose solution with both the vehicle and nicotine in an effort to increase palatability, with the difference between nicotine and vehicle solutions indexing the reinforcing effects of nicotine.<sup>96</sup>

Although methods may vary, oral self-administration of nicotine has been used to demonstrate genetic influences on nicotine intake in mice. Strain surveys

of inbred mice demonstrate that genetic variance contributes to differences in oral nicotine self-administration. C57BL/6 mice show a higher preference for oral nicotine than do DBA/2 mice in a two-bottle-choice paradigm;<sup>98</sup> the C57BL/6 mice also show greater preference for ethanol and amphetamine, and the DBA/2 show greater preference for aspartame. In an extensive strain survey of oral nicotine consumption using the two-bottle-choice test, the C57BL/6 strain consumed the most nicotine, followed in order of descending consumption by DBA/2 > BUB > A ≥ C3H ≥ ST/b mice.<sup>99</sup> Another strain survey compared oral nicotine self-administration in the following strains of mice: A/JxNMRI cross, C57BL/6, C3H/J, DBA/2, NMRI, ST/bJ; as in a study by Robinson and colleagues,<sup>99</sup> the C57BL/6 mice consumed the most nicotine and the ST/bJ mice consumed the least.<sup>100</sup> Strain survey results provide important information to guide the appropriate selection of experimental subjects on the basis of the research question and also provide important information for future genetic analysis.

Work from Collins's laboratory identified a single nucleotide polymorphism in the gene that codes for the  $\alpha 4$  nAChR subunit, *CHRNA4*, that results in either alanine or threonine at position 529 on the  $\alpha 4$  protein.<sup>101</sup> This polymorphism alters  $\alpha 4$  nAChR function and sensitivity to the behavioral effects of nicotine.<sup>101–103</sup> To test whether the *CHRNA4* polymorphism alters nicotine preference, choice of nicotine consumption was compared across 14 strains of mice that differed in expression of the *A529* versus *T529* variant.<sup>104</sup> Strains with the *A529* variant of *CHRNA4* had significantly lower levels of nicotine consumption. Consistent with human data,<sup>20,23,24</sup> these results demonstrate that an altered sequence of *CHRNA4* influences nicotine intake and, thus, could influence development and persistence of nicotine dependence.

Using data indicating that C57BL/6 mice show high levels of nicotine consumption and ST/b mice show low levels of nicotine consumption, a study investigated if alterations in expression of *Cyp2a5*—the homologue of the human gene *CYP2A6*, which codes for an enzyme involved in the metabolism of nicotine—were related to oral nicotine self-administration in mice.<sup>105</sup> F2 mice from a C57BL/6 and ST/b cross were segregated into high- and low-nicotine consumers, and levels of *Cyp2a5* protein were analyzed.<sup>105</sup> In male F2 mice, the high nicotine consumption was associated with higher levels of *Cyp2a5* protein and faster nicotine metabolism. This corresponds well with what is seen in smokers: smokers with a null *CYP2A6* allele smoke less and smokers with a duplicate copy of *CYP2A6* smoke more than do homozygous wild-type smokers.<sup>106</sup>

The preclinical studies described above provide strong evidence for a biological basis of nicotine reinforcement—one key criterion for an endophenotype. In addition, evidence for strain differences in nicotine reinforcement paradigms supports the search for specific candidate genes and pathways that may underlie nicotine reinforcement measures in humans. Studies documenting effects of genetic and pharmacological manipulation on nicotine reinforcement in animal models point to specific candidate genes that can be tested for association in human studies.

### **Reinforcement-Enhancing Effects of Nicotine**

Before proceeding to the overview of human research on nicotine reinforcement, it is important to note that nicotine may have a second reinforcing function, aside from the direct (primary) reinforcing effects noted above. As noted previously, stimuli accompanying nicotine infusions can become secondary reinforcers through their association with nicotine (i.e., cues). However, animal studies show that nicotine can enhance the reinforcing value of other

reinforcers *not* associated with nicotine intake. In this work, primarily conducted by Caggiula and colleagues (e.g., Chaudhri, et al. 2006<sup>107</sup>), nicotine has been shown to enhance responding for reinforcement from stimuli, such as a light offset (darker environments are preferred by rodents), that are available independent of the responses for nicotine. In other words, in addition to the stimuli associated with nicotine infusion becoming secondary reinforcers that enhance responding for nicotine,<sup>78</sup> nicotine can enhance responding for other reinforcing stimuli, showing a dual reinforcing function. Nicotine's "reinforcement-enhancing" effects differ from the secondary reinforcing effects of cues in that the latter develop through associative processes requiring a contingency between the cues and nicotine administered in rapid fashion, while the former are nonassociative and can occur regardless of nicotine delivery speed.<sup>107</sup> Later work suggests that the reinforcing-enhancement effects of nicotine may occur in humans;<sup>108</sup> inadequate study of this phenomenon in humans, however, does not allow for extensive discussion of the potential for measures of the reinforcement-enhancing effects of nicotine as endophenotypes. However, this influence warrants greater attention in the broader field to help explain why smoking appears to acutely increase consumption of other reinforcers, such as alcohol.<sup>109</sup> It also may contribute crucially to understanding why smoking is so difficult to quit. Quitting smoking would remove not only the direct reinforcing effects from smoking, as is commonly the sole focus, but also these reinforcement-enhancing effects. This would lead to a lessening of reinforcement from many other reinforcers, causing greater deprivation than might be expected based on the observed direct reinforcing effects of nicotine.

### **Human Clinical Research**

Additional evidence for biological plausibility of reinforcement measures as potential

endophenotypes comes from research linking clinical (self-report) measures of the amount and persistence of smoking reinforcement with the outcome of a subsequent quit attempt. Poorer outcome of a quit attempt is typically determined by faster time to relapse (i.e., shorter duration of abstinence), and secondarily, by more severe withdrawal. These results support the notion that objective (i.e. non-self-report) measures of smoking amount and persistence may be candidate endophenotypes.

The amount, or *frequency*, of cigarette consumption typically is assessed simply by self-report of number of cigarettes per day during “maintenance,” or when not attempting to cut down or quit. Greater number of cigarettes per day has been related to poorer outcome of a quit attempt (i.e., greater dependence) in that amount of smoking is often related to greater severity of withdrawal and to shorter time to relapse after a quit attempt.<sup>110</sup> Measures of smoking *persistence* are also relevant, such as time to first cigarette of the day after waking; longer times are related to lower levels of dependence. While smoking frequency and persistence are not interchangeable (i.e., measure the same thing), they are also not independent in that greater amount of smoking is associated with faster time to first cigarette and shorter duration of prior quit attempts.<sup>111</sup> In any case, across various types of clinical trials or among self-quitters, a greater number of cigarettes per day (frequency) and faster time to first cigarette of the day (greater persistence) before quitting are associated with poorer cessation outcome—notably, shorter duration of abstinence and greater severity of withdrawal symptoms.<sup>112–114</sup> Note that self-reported number of cigarettes per day and time to first cigarette are two items from the FTND self-report dependence measure<sup>3</sup> that are most predictive of cessation outcome; together, they are sometimes used as the Heaviness of Smoking Index dependence measure.<sup>3</sup> Those high on this index are less

able to quit, even for 24 hours, compared to those low on this index.<sup>115</sup>

After starting a quit attempt, any smoking at all (a lapse) strongly predicts eventual relapse, further illustrating the importance of smoking persistence (inability to refrain from smoking) as an index of dependence. This effect is very pronounced if the smoking occurs on the quit day itself (very strong smoking persistence),<sup>116</sup> but remains strong even if it occurs after weeks of maintaining abstinence, whether with or without cessation medication.<sup>113,117,118</sup> Smoking persistence appears to be a stable characteristic in that the faster a smoker resumes smoking (relapses) during a prior quit attempt, the greater the chances of relapsing during a subsequent quit attempt.<sup>113</sup> Those who have never tried to quit at all (no prior demonstration of ability to refrain from smoking) also are typically less successful when they try to quit.

As suggested, smoking frequency can predict persistence during a given quit attempt in that those who smoked more cigarettes per day before quitting are more likely to lapse on the quit day or soon after quitting.<sup>117</sup> Some studies have shown that after having quit, the amount (i.e., frequency) of smoking during the first lapse predicts faster occurrence of the second lapse and perhaps risk of full-blown relapse.<sup>119</sup> In sum, whether before or after the quit attempt, self-report measures of frequency and persistence of smoking predict poorer outcome of a quit attempt, a key index of dependence.

### ***Description of Potential Endophenotype Measures of Nicotine or Smoking Reinforcement***

“Reinforcement” is a broad concept that is characterized by several dimensions and cannot be captured by a single measure,<sup>53,120</sup> as evidenced by the separate consideration above of smoking frequency versus

persistence. Various short-term objective measures of reinforcement, and what they purport to assess, are outlined here. Some capture smoking frequency (e.g., ad lib self-administration), while others may reflect smoking persistence (e.g., progressive ratio). One approach, behavioral economics, may be able to model both. “Drug choice” is a separate concept that is not generally captured by dependence criteria of smoking frequency or persistence but that has been shown to relate to dependence in laboratory studies. Drug choice (i.e., nicotine preference) is the degree to which drug-containing substances are preferred over otherwise equivalent nondrug substances (e.g., placebo cigarettes). All of these procedures are derived from research on nicotine and other drugs of dependence with nonhuman animals. The biggest limitation of these measures of reinforcement is uncertain generalizability to smoking behavior in the natural environment.

### **Ad Libitum (ad lib) Drug Self-Administration**

In the natural environment, nicotine delivery is usually accomplished with a fairly simple response—that is, puffing on a cigarette once it is lit (although more extensive behavior may be required to obtain the cigarettes). Thus, observation of smoking behavior, or ad lib self-administration, over a specific period of time may have the strongest face validity as an objective measure of reinforcement. A variation, adopted from animal research (described above), involves requiring the subject to make one response (e.g., pressing a computer key) that is reinforced by one unit of drug (e.g., a puff). This procedure assesses smoking intensity, amount (or rate) of consumption, or simple drug-taking behavior,<sup>53</sup> similar to the self-reported number of cigarettes per day.

Smoking consumption in the laboratory can be assessed by simply counting the number of cigarettes or individual puffs (usually from videotapes of the subjects). Consumption can also be measured indirectly by biochemical

indices of recent smoking exposure, such as blood nicotine level or expired-air carbon monoxide boost from before to after the session.<sup>121</sup> The reliability of behavioral observation of smoke puffs is very high because it is a rather discrete behavior.<sup>122</sup> The test-retest reliability of measures of ad lib smoking also tends to be high. In unpublished analyses, the authors of this chapter examined the correlation of puffs taken during a brief ad lib smoking period on each of two days in 54 smokers who had abstained overnight. The number of puffs correlated 0.67 ( $p < .001$ ) between sessions, although latency to first puff, a measure of persistence, was not significantly correlated between sessions (0.18). This difference in reliability suggests that smoking persistence (as measured by latency to first puff) may be less reliable, and also, that persistence and frequency (as measured by total puffs) may capture different aspects of smoking reinforcement. Use of smoking topography devices, particularly the Clinical Research Support System,<sup>123</sup> can also provide an objective assessment of intake by quantifying puff volume, puff duration, interpuff interval, and puff velocity.<sup>124</sup> Amount of consumption of nicotine per se can also be assessed by providing smokers with novel nicotine delivery methods, such as nicotine spray or intravenous infusion, and perhaps gum.<sup>122,125,126</sup>

A variation on this procedure is to require more than one response per drug unit received, such as providing one drug unit for every 5 or 10 responses, as commonly done in animal research (e.g., fixed ratio or variable ratio, reinforcement schedules; see also subsections on “Behavioral Economics” and “Progressive Ratio Measures” below). The greater the response requirement, the more drug-motivated behavior generated, up to a point. (Another variation that requires large amounts of responding and that exploits the important motivating effects of drug cues is the second-order schedule, which is not discussed here in detail, given its



rarity in human studies.) Beyond a certain point, the amount of responding required for a unit of drug becomes so great that self-administration is discouraged; this is essentially a means to assess persistence. This “breakpoint” is the key measure in the progressive ratio procedure, as discussed later, and is an important index of the reinforcing value of the drug.

While amount of ad lib smoking in a laboratory session appears to have face validity, relatively little effort has been made to show that those who smoke more under such conditions also smoke more outside the laboratory on a day-to-day basis. A more specific limitation of this approach is that drug satiation can occur quickly in even a brief laboratory session, thereby resulting in little subsequent drug-motivated behavior. Low rates of such behavior complicate the interpretation of comparisons between individuals in intensity of self-administration. This problem is reduced by use of schedules requiring multiple responses per reinforcement, noted previously. A third limitation is that because cigarettes contain much more than just nicotine (most substance abuse involves more than one component), self-administration of cigarettes does not necessarily index the reinforcing effects of nicotine per se (see “Nicotine Choice” below). Use of these procedures with novel nicotine delivery methods can determine nicotine reinforcement.

### **Nicotine Choice**

The nicotine choice procedure more specifically addresses the degree to which the drug nicotine is reinforcing.<sup>127</sup> This procedure compares self-administration of one substance that contains a drug with another that is identical except for containing no drug (i.e., a placebo) and is analogous to use of active versus inactive lever pressing in animal studies, described previously. Here, the absolute levels of self-administration, or intensity, are not of primary interest, but rather, the difference in self-administration

between drug and placebo. Greater self-administration of the former versus the latter indicates that the drug itself is reinforcing. This procedure essentially assesses preference between two alternatives, one containing a drug and the other not, and it controls for virtually all nonpharmacological aspects of substance use (e.g., responses to conditioned cues), isolating the pharmacological effects. When choice is compared between conditions or groups, differences reflect the relative reinforcing value of nicotine (*relative* means greater choice in one condition or group versus the other, even if neither or both choose nicotine more than placebo). When the two substances are made available ad lib, this is often called a *concurrent choice procedure*.<sup>122</sup>

Because subjects may vary markedly in overall drug self-administration frequency, comparisons of drug choice may be difficult between subjects. One common way to reduce this problem is to standardize the procedure by requiring a fixed number of choices (forced choice), spaced apart to avoid satiation, and determine whether the drug is chosen more often than the placebo.<sup>127,128</sup> This approach is described in chapter 8; it is perhaps the only self-administration procedure that can be used with naive individuals with no prior experience with the drug. Other variations on choice can involve different drug doses (e.g., high-versus low-nicotine cigarette) or substances differing on other characteristics of interest (e.g., nicotine by nasal spray versus gum).

A limitation of this measure is that interpretation of results can be unclear. Choice of drug versus placebo is a function of the specific procedures—namely, the dose per drug use and the number of choices provided. Because drugs often have toxic or satiating effects, drug choice will be less as dose per administration and number of choices increase. Thus, whether or not the drug is chosen more than the placebo is specific to the procedures used, and



choosing the drug less than the placebo does not necessarily mean that the drug is not reinforcing. It is the relative difference in choice between conditions or individuals that is the important measure.

### Behavioral Economics

Drug use in the natural environment can require more than a single simple response and may require engaging in extensive behavior (e.g., having to go outside to smoke at work, walking through snow to a store that sells cigarettes). Behavioral economics is one standard approach to determining how different response requirements for a drug affect intake. See Bickel and colleagues<sup>129,130</sup> and Perkins and colleagues<sup>131</sup> for a more thorough discussion of this approach. Typically, the number of responses (price) required per drug unit is manipulated, so that consumption of drug (demand) across increasing prices can be determined, forming a price-demand curve. Across low to moderate prices, consumption is usually maximal and unchanged, producing a curve that is flat in that responding can easily increase to meet the increasing behavioral prices of smoking. Demand is said to be inelastic, or unchanging, with respect to price, and responses here may reflect the individual's typical smoking frequency. At higher prices, however, responding continues to increase up to a point to meet increasing price, but responding eventually slows and consumption decreases (i.e., becomes elastic), indicating a limit to the price that a given individual will pay for the drug.

The higher this maximum behavioral price a subject will pay, the higher the maximum reinforcing value of the substance (similar to the breakpoint in the progressive ratio procedure), which may also reflect smoking persistence. Such an approach can comprehensively characterize differences in drug reinforcement due to various acute (e.g., medication) or chronic (e.g., individual differences in dependence) factors.<sup>131</sup>

For example, the price-demand curve may decrease across all prices (i.e., in parallel fashion), indicating an overall reduction in *frequency* of drug use and a drop in the reinforcing value of the drug. Alternatively, the price-demand curve may shift to the left, indicating that the demand for the drug is unaffected at most prices, but decreases only at high prices, such that the maximum price is smaller. This shift would suggest a selective drop in the maximum reinforcing value of the drug, but not an overall drop in the drug's reinforcing value, since responding does not change at lower prices. This outcome also indicates a decrease in the *persistence* of drug use. An important variation of this procedure involves examining changes in the price-demand curve as a function of the availability of alternative reinforcers, since drug use often involves choosing between the drug versus some alternative, such as money (e.g., buying cigarettes is a choice of cigarettes over money). Comparing the influence of various alternative reinforcers is a central focus of the behavioral economics approach because the price-demand curve can shift to the left if an attractive alternative is present.

This approach has some limitations. Obtaining the data to construct price-demand curves can be time-consuming in that a separate session may be needed to determine consumption at each given price, unless actual consumption is kept low to prevent satiation. (Otherwise, reduction in consumption caused by satiation will confound assessment of the reinforcing effects of smoking under conditions presented later in the session). Whether greater responding of the type required in laboratory sessions (e.g., pressing a computer key) corresponds to greater responses to obtain the drug in the natural environment is not known.

### Progressive Ratio Measures

A key aspect of dependence is the persistence of drug use despite its costs. As described

above, persistence is commonly and directly assessed by determining the maximum amount of responses the individual will engage in for one unit of the drug. Formal behavioral economics approaches can have practical limitations, as noted, such as requiring multiple sessions to determine price-demand curves, with a single price, or reinforcement schedule, per session. The progressive ratio (PR) procedure provides a way to assess maximum price, or persistence, more efficiently, although it cannot also assess frequency, as can behavioral economics. In the PR procedure, the number of responses required per reinforcement (e.g., one puff) increases *within* the session, after each earned reinforcer, until the point at which responding for the drug is not maintained. The response requirement at that point, termed the “breakpoint,” is believed to index persistence of drug use, or incentive motivation.<sup>53</sup> The increase in response requirement is usually rapid (e.g., 30%–50% higher than prior requirement) to limit actual drug intake so that drug satiation does not interfere with assessment of maximum price (persistence). The breakpoint for smoke puffs is significantly associated with the maximum price paid for smoking (number of responses for one drug unit) in a behavioral economics paradigm,<sup>132</sup> consistent with the notion that both reflect smoking persistence. Moreover, PR breakpoint is not related to choice measures, consistent with the notion that they tap different facets of reinforcement.<sup>132</sup>

PR procedures have some limitations. First, the breakpoint, or highest completed reinforcement schedule, is a nonparametric measure, rather than a continuous measure, since only specific schedules of reinforcement are set. Thus, the number of these schedules completed, or reinforcers earned, is the dependent measure of interest. Because satiation must be avoided to allow a true measure of the breakpoint, the number of earned reinforcers must be small. One consequence of this procedure

is that statistical power can be limited in comparisons of breakpoints between individuals or conditions. Secondly, as in behavioral economics, whether greater responding of the type required in laboratory sessions corresponds to greater drug-seeking responses in the natural environment is not known.

### ***Genetic Influences on Measures of Smoking Reinforcement in Humans***

Although there is ample evidence supporting the heritability of nicotine dependence as assessed by self-report measures (chapter 2), no studies were found that parse out the relative contribution of genetic influences to laboratory-based measures of nicotine or smoking reinforcement. Despite this critical gap in the literature, evidence for rodent strain differences in nicotine self-administration and results of transgenic mouse studies (described above) provide a strong biological rationale for investigating the role of specific genetic factors in objective behavioral measures of smoking reinforcement. As far as known, only two studies have examined this question in humans.

As discussed above, individuals with low- or null-activity genetic variants of the nicotine-metabolizing enzyme CYP2A6 tend to smoke fewer cigarettes per day by both self-report and biochemical measures.<sup>17</sup> To extend this assessment to objective laboratory-based measures of consumption, Strasser and colleagues<sup>133</sup> compared smoking topography indices in normal versus genetically slow nicotine metabolizers on the basis of the *CYP2A6* genotype. Smokers carrying reduced- or null-activity *CYP2A6* alleles (slow metabolizers) had significantly lower puff velocities than did normal metabolizers, controlling for gender and cigarette nicotine level. However, as discussed below, the relationship of smoking topography to nicotine dependence has not been thoroughly investigated.

A second study examined genetic associations with the relative reinforcing value of nicotine, as measured by a nicotine cigarette choice paradigm.<sup>134</sup> This analysis focused on the role of the functional *OPRM1* gene *A118G* variant and is based on preclinical evidence that nicotine reward is, in part, mediated by mu opioid receptors<sup>135</sup> and on clinical data supporting an association of this variant with smoking cessation.<sup>40</sup> In this double-blind, cross-over study, 60 smokers (30 with the *OPRM1* wild-type *AA* genotype and 30 with at least one reduced-activity *\*G* allele) participated in the nicotine cigarette choice paradigm following either four days of the mu opioid antagonist naltrexone or a placebo (order of study medication counterbalanced with a five- to seven-day washout period). This paradigm provided a choice between puffs of a denicotinized cigarette and a 0.6-mg nicotine cigarette over a three-hour period. The results revealed a significant *OPRM1* genotype by gender interaction. Among females, those with a reduced activity *OPRM1* *\*G* allele self-administered only 50% of puffs from the nicotine cigarette (and the other 50% from the denicotinized cigarette), compared to smokers with the *AA* genotype who took about 75% of puffs from the nicotine cigarette. Males, regardless of genotype, took about 75% of puffs from the nicotine cigarette. Secondary exploratory analyses from this study suggest that effects of *OPRM1* may be modified by genetic variation in the intracellular-signaling cyclic adenosine monophosphate–response element binding protein CREB1,<sup>136</sup> an effect consistent with preclinical research.<sup>135</sup>

A later study examined genetic factors associated with the increase in ad lib smoking due to negative versus positive mood, as well as moderating influences of actual or expected nicotine content of cigarettes.<sup>137</sup> The increase in ad lib smoking amount due to negative mood was associated with *DRD2* *\*C95T* (*CC* > *TT* or *CT*), *SLC6A3* (presence of *\*9*-repeat > absence

of *\*9*-repeat), and among those given a nicotine cigarette, *DRD4* (presence of *\*7*-repeat > absence of *\*7*-repeat) and *DRD2/ANKK1* *\*TAQIA* (*TT* or *CT* > *CC*). Although no genetic studies were found using behavioral economics measures in smokers, there are data to support the role of specific polymorphisms in the relative reinforcing value of alcohol.<sup>138</sup>

## **Relation of Smoking Reinforcement Measures to Dependence**

### **Ad Lib Smoking**

The relationship of ad lib smoking measures to nicotine dependence has been explored in very few studies. One way of approaching this is to determine whether ad lib smoking is sensitive to nicotine deprivation. For example, Perkins and colleagues<sup>139</sup> administered a placebo or 15 or 30 micrograms (μg)/kg nicotine by nasal spray every 30 minutes for 2.5 hours in smokers who had abstained overnight and found a dose-dependent decrease in ad lib puffs, cigarettes, and carbon monoxide boost from baseline. However, ad lib smoking may not be sensitive to slower methods of nicotine delivery, such as the nicotine patch.<sup>140</sup> Other procedural factors can moderate the sensitivity of this measure to pretreatment manipulations and medication.<sup>141</sup> In a more direct association with dependence, one study found that pretreatment assessment of a very specific smoking topography measure of ad lib smoking—that is, typical size of puffs—predicts smoking cessation outcome in an NRT trial.<sup>124</sup> It is likely that the shorter the ad lib smoking period in a laboratory session, the weaker the expected link between smoking during that period and indices of dependence, given the restricted duration of smoking being sampled.

### **Nicotine Choice**

Choice procedures have been used in a growing number of studies relating nicotine choice to some indices of dependence or to other manipulations of interest. Greater

choice of nicotine over placebo spray has been found in dependent smokers versus nonsmokers or former smokers, whether by nasal spray<sup>128</sup> or gum.<sup>142</sup> However, questions about the relation of choice to dependence remain, as dependent and nondependent smokers did not differ in nicotine choice in one study.<sup>128</sup> Increasing the dose of the nicotine choice or extending the duration of the session may make this procedure more sensitive to differences in reinforcement between dependent and nondependent smokers. Nicotine choice (via gum) is greater in alcoholic smokers than in nonalcoholic smokers, who also differ in other indices of dependence, such as difficulty in quitting.<sup>143</sup> In addition, those who self-administer more nicotine than a placebo spray in a concurrent choice procedure also self-report smoking more cigarettes per day and tend to take more puffs from their preferred brand during a laboratory assessment of ad lib smoking.<sup>122</sup>

These results suggest that greater nicotine versus placebo spray choice in this laboratory procedure is associated with a generally greater frequency of smoking intake in the natural environment. Overnight abstinence from smoking in dependent smokers increases choice of nicotine over placebo, whether by cigarette or nasal spray.<sup>127</sup> This influence of brief abstinence has also been shown when subjects were freely able to adjust nicotine intake independent of puff number via a smoke mixing device drawing smoke from nicotine versus denicotinized cigarettes.<sup>144</sup> Most important, choice of nicotine over placebo nasal spray in a forced choice procedure assessed before a quit attempt predicts greater severity of withdrawal in the week after quitting and faster time to relapse.<sup>145</sup> Thus, greater choice of nicotine versus placebo substances in this laboratory procedure has been associated with various indices of dependence and may serve as a promising endophenotype of dependence after chronic smoking exposure.

### Behavioral Economics

Overnight abstinence increases responding for smoking versus the alternative of money,<sup>122,146,147</sup> indicating greater frequency of smoking due to abstinence. Availability of nicotine gum may modestly attenuate responding for smoking,<sup>130</sup> further showing that nicotine deprivation can increase measures of smoking reinforcement via behavioral economics procedures. However, as far as known, neither the overall demand for smoking (frequency) nor the maximum price smokers will pay for smoking (persistence) before a quit attempt has been related to the outcome of that subsequent quit attempt.

### PR Measures

As with prior procedures, overnight abstinence increases responding on a PR for smoke puffs.<sup>148</sup> The amount of responding on a PR for smoke puffs is greater for nicotine versus placebo cigarettes under some but not all conditions and in most but not all smokers.<sup>148</sup> For example, PR responses were greater for nicotine versus denicotinized cigarettes when the two were concurrently available, but much less so when they were available independently in different sessions, particularly in women.<sup>149,150</sup> Yet, pretreatment with nicotine spray or patch only slightly and nonsignificantly reduces the breakpoint of responding for smoke puffs in smokers not trying to quit.<sup>151</sup> Failure of nicotine pretreatment to alter the breakpoint for smoking is not unique to PR assessment; it has been seen with ad lib smoking and other reinforcement measures.<sup>139,141</sup>

### Smoking Reward

The definition of *reward* and its distinction from reinforcement and mood effects of smoking are discussed in the last part of chapter 8 (“Initial Nicotine Sensitivity Endophenotypes: Summary and Future Directions” section). In humans, reward reflects the hedonic value of a substance,

or the subjective evaluation of the substance's incentive motivating effects.<sup>53</sup> Its measurement, as with reinforcement, requires consumption of a substance, while most other self-report measures obtained in drug research (e.g., mood, craving) do not. Below, preclinical evidence is discussed supporting the biological plausibility of a genetic basis for nicotine reward, followed by discussion of measurement, genetic influences, and relation to dependence in human populations. Because there does not appear to be an "objective," non-self-report measure of smoking reward in humans, the utility of self-reported reward in predicting dependence will be examined.

## ***Biological Plausibility***

### **Preclinical Research**

In contrast to the self-report measures of reward in humans, measures thought to reflect drug reward in animals are behavioral and, thus, potentially "objective," by necessity. The most widely used assessment of drug reward in animals is the conditioned place preference (CPP) paradigm. In CPP, drug administration is paired with a novel environment, and vehicle administration is paired with a second novel environment in a place-conditioning chamber. The time spent in the environment previously paired with a drug is used as a measure of the rewarding properties of the drug (i.e., it is assumed that spending more time in the environment associated with experiencing the effects of the drug indicates that the environment has acquired positive effects through its association with the drug). Rodents develop CPP for nicotine.<sup>135,152–157</sup>

Another measure believed to index reward is intracranial self-stimulation (ICSS). Rats can be readily trained to self-administer electrical stimulation of the lateral hypothalamus or medial forebrain bundle. It is believed that this stimulation is self-administered because it activates the underlying neural circuit involved

in reward.<sup>158</sup> Drugs that are reinforcing generally lower the current sufficient to sustain ICSS (i.e., the threshold current), indicating that lower thresholds reflect pleasure states. By contrast, withdrawal from these drugs after chronic exposure often raises the ICSS threshold, which is believed to reflect aversive states.<sup>158</sup> In rats trained to ICSS, systemic administration of nicotine decreased the threshold current for ICSS by approximately 20%, indicating that nicotine results in pleasure states and so is rewarding,<sup>159</sup> while abstinence from nicotine has been shown to raise the ICSS threshold.<sup>160</sup>

A review of studies using CPP and ICSS suggests that ICSS and CPP may have different neurobiological substrates. Work by Panagis and colleagues<sup>159</sup> and Kenny and Markou<sup>160</sup> suggest that the effects of nicotine on ICSS involve both low-affinity (e.g.,  $\alpha 7$  nAChRs) and high-affinity (e.g.,  $\alpha 4\beta 2$ ) nAChR subunits. In contrast, Walters and colleagues<sup>161</sup> found that low-affinity  $\alpha 7$  nAChRs were not necessary for nicotine CPP, but  $\beta 2$  subunits were critically involved in this behavior. It is possible, however, that  $\alpha 7$  nAChRs may modulate the effects of  $\beta 2$ -containing nAChRs on ICSS. In support, Mameli-Engvall and colleagues<sup>162</sup> found that  $\beta 2$ -containing nAChRs in the VTA mediated changes in the resting state of VTA dopaminergic cells from inactive to active, suggesting a critical role of  $\beta 2$ -containing nAChRs in dopamine release. The  $\alpha 7$  nAChRs also modulated the active state of the dopamine neurons, but the  $\alpha 7$  nAChRs were only effective after activation of  $\beta 2$ -containing nAChRs. In other words, the rewarding effects of nicotine could be expressed independently of  $\alpha 7$  nAChRs but, depending upon conditions,  $\alpha 7$  nAChRs could also be involved in changing nicotine-stimulated dopamine release related to reward. Thus, CPP and ICSS may measure different aspects of the rewarding effects of nicotine because different nAChR subtypes appear to be involved.



Genetic approaches such as strain surveys have been useful in identifying (1) natural genetic variance that contributes to differences in CPP, (2) receptors involved in CPP, and (3) how polymorphisms in genes encoding those receptors could alter nicotine intake. In a study comparing nicotine CPP in C57BL/6 versus DBA/2 mice, C57BL/6 mice but not DBA/2 mice developed CPP.<sup>154</sup> These results match those of oral nicotine self-administration that reported higher levels of self-administration in the C57BL/6 mice compared to DBA/2 mice.<sup>98–100</sup>

Knockout models provide further evidence for genetic influences on nicotine reward. In one study, infusion cannula were implanted into the VTA of wild-type and  $\beta 2$  nAChR subunit knockout mice before training on a task that combined place conditioning and self-administration.<sup>163</sup> Mice were trained to associate one arm of a Y-maze with VTA infusion of nicotine. The wild-type but not  $\beta 2$  knockout mice showed greater preference for nicotine as measured by an increase in time spent in the arm of the maze associated with nicotine infusions. In addition, systemic administration of nicotine increased dopamine levels in the nucleus accumbens in wild-type but not  $\beta 2$  knockout mice, providing a neurochemical mechanism for these genetic effects on reward. Further support for  $\alpha 4\beta 2$  nAChR involvement in nicotine reward comes from a study that investigated CPP in mice with a single point mutation that results in an increase in sensitivity of  $\alpha 4$ -containing nAChRs. The  $\alpha 4$  mutant mice showed dramatically increased sensitivity for the development of CPP; wild-type mice developed CPP with a dose of 500  $\mu\text{g}/\text{kg}$ , while the  $\alpha 4$  mutant mice developed CPP with a 10  $\mu\text{g}/\text{kg}$  dose of nicotine.<sup>164</sup> Not only does this study strongly suggest that  $\alpha 4\beta 2$  nAChRs are involved in the rewarding properties of nicotine but also demonstrates how a polymorphism of the gene coding for the  $\alpha 4$  nAChR subunit could alter the threshold for developing nicotine dependence.

Polymorphisms in genes related to other neurotransmitter systems may also contribute to nicotine intake. For example, adenosine<sub>2A</sub> ( $A_{2A}$ ) knockout mice did not develop nicotine CPP nor have increased extracellular levels of dopamine in the nucleus accumbens after nicotine treatment. In addition, cannabinoid (CB1) receptor knockout mice did not develop CPP for nicotine.<sup>165</sup> However, in another study, CB1 knockout mice and wild-type mice showed similar levels of IV nicotine self-administration,<sup>166</sup> suggesting that CPP (i.e., reward) and IV self-administration (i.e., reinforcement) may be mediated by different cellular and genetic processes. As suggested in the introduction to this chapter, these data support the notion that reward and reinforcement are different constructs from a biological and behavioral perspective.

Opioid receptors may also mediate the rewarding properties of nicotine. In preproenkephalin knockout mice, no CPP was seen compared to wild-type mice.<sup>167</sup> In addition, mu opioid knockout mice have deficits in nicotine CPP.<sup>168</sup> Furthermore, nicotine CPP is absent in CREB <sup>$\alpha A$</sup>  mice, consistent with new human data associating CREB1 and the human *OPRM1* receptor gene with individual variation in nicotine reward.<sup>134,136</sup>

Genetic vulnerability to the effects of nicotine on locomotion may also predict genetic susceptibility to the rewarding properties of nicotine. Two lines of mice were generated from a heterogeneous stock: in one line, nicotine depressed locomotor activity; in the other, nicotine increased locomotor activity. The two lines were tested for nicotine CPP; the line in which nicotine depressed locomotor activity showed less CPP than the line in which nicotine increased locomotor activity.<sup>169</sup> These results suggest that genetic influences that mediate the psychostimulant properties of nicotine also mediate the rewarding properties of nicotine.



Studies in rats also demonstrate the involvement of genetics in the rewarding properties of nicotine as measured by CPP. F344 rats and Lewis rats were compared for development of CPP for nicotine.<sup>170</sup> After five trials, the Lewis rats showed CPP, but the F344 rats did not. When training was extended to 10 trials, Lewis rats still showed CPP for nicotine, but the F344 rats showed conditioned place aversion. Similar results were found in another study: Lewis rats showed CPP, but F344 rats did not.<sup>171</sup> It is interesting to note that for IV nicotine self-administration, neither F344 rats nor Lewis rats self-administered nicotine.<sup>86</sup> The difference in results could be due to methodological differences or further demonstration that reward, as measured by CPP, and reinforcement, as measured by IV self-administration, are largely independent facets of nicotine's motivational effects and are mediated by different genetic substrates.

### **Description of the Measurement of Nicotine Reward in Humans**

Objective measures of reward in humans that could potentially serve as endophenotypes similar to CPP and ICSS in animals have not been identified, leaving only self-report measures for evaluation. Typical measures relevant to reward in humans are self-report ratings of “liking,” “satisfying,” “good effects,” or “bad effects” that are completed following consumption of the substance. Items reflecting reward are included in several self-report measures, including the Cigarette Evaluation Scale of Rose and colleagues,<sup>172</sup> which perhaps is the most widely used measure of hedonic and sensory effects of smoking. Items include asking how much did the subjects “like” the puffs they just took and how “satisfying” they were, along with other questions not pertaining to reward, such as how high in nicotine or similar to their own brand the puffs were (items that do not directly reflect the cigarette's hedonic value). Because of limited data on reliability of these measures,

the authors of this chapter examined test-retest consistency of ratings of “liking” and “satisfying” of puffs in a study of 54 smokers who smoked the same brand of cigarettes on two days, each following overnight abstinence (unpublished data). Subjects took four puffs in controlled fashion before one set of ratings and then smoked the cigarette ad lib for 14 minutes before a second set of ratings. The ratings of “liking” and “satisfying” of the four controlled puffs correlated .58 and .59, respectively (both  $p < .001$ ), between sessions, while the same ratings of the cigarettes after ad lib smoking correlated .55 and .50, respectively (both  $p < .001$ ), between sessions. Thus, these reward ratings are highly reliable.

### **Genetic Influences on Measures of Nicotine Reward in Humans**

No investigations were found of the heritability of the self-reported rewarding or other hedonic effects of smoking, and only limited data on specific genetic associations with this outcome were identified. For example, in the study of nicotine choice by *OPRM1* genotype described above,<sup>134</sup> participants also completed the Cigarette Evaluation Scale and Sensory Questionnaire<sup>172</sup> following initial exposure to the two research cigarettes: 0.05-mg (denicotinized cigarette) and .6-mg nicotine cigarette. The difference in ratings of the two cigarettes served as a measure of the rewarding effects of nicotine per se, and not simply of smoking, and was examined by the *OPRM1* genotype. Consistent with the finding of a reduced nicotine choice among smokers carrying the *OPRM1* low-activity \*G allele, noted earlier, these smokers reported significantly smaller differences in ratings of satisfaction (and “strength”) between the nicotine and denicotinized cigarettes. In a study described earlier,<sup>137</sup> which examined increased smoking behavior and reward due to negative mood, the increase in smoking reward (“liking”) was associated

with *DRD2/ANKK1\*TAQ1A* (*TT* or *CT* > *CC*) and *OPRM1* (*AA* > *AG* or *GG*).

### ***Association of Nicotine Reward Measures with Dependence***

Smoking reward in humans is a focus of acute laboratory-based manipulations, such as medication pretreatment, but generally has not been studied prospectively in cessation trials. An exception is a study by Shiffman and colleagues<sup>119</sup> in which greater hedonic rating (“pleasantness” of cigarette and “satisfying” averaged together) of the cigarette smoked during the first lapse after quitting predicted greater speed of a second lapse and eventual relapse. Yet, nicotine versus placebo patch did not reduce the hedonic rating of the lapse cigarettes, even though the nicotine patch slowed progression from first to second lapse. Another study suggested that higher ratings of the positive effects of nicotine nasal spray at pretreatment predicted subsequent abstinence in a nasal spray open label trial.<sup>173</sup> However, in a cross-sectional comparison, ratings of nicotine spray reward did not differentiate dependent and nondependent smokers.<sup>174</sup> Thus, some data support the association of smoking reward before quitting with success of a subsequent quit attempt (i.e., dependence).

## **Acute Smoking or Abstinence Effects on Cognitive, Affective, and Physiological Function**

Although research clearly shows that smoking in general, and nicotine in particular, is reinforcing, and that this reinforcing effect is key to dependence, *why* smoking is reinforcing remains uncertain. A variety of the effects of smoking or its

abstinence may contribute to the motivation to self-administer nicotine in chronic smokers. For example, smoking may be motivated either by the desire to enhance cognitive functioning and performance or to relieve negative mood. Examples of this include nicotine’s effects on sensory processing, cognitive function (i.e., attention and working memory), affective regulation, and impulse control. However, as a consequence of chronic smoking and neural adaptations, abstinence from nicotine can also produce decrements in these domains. Subsequently, smoking relieves these symptoms very reliably, resulting in negative reinforcement of smoking behavior (i.e., smoking-elicited relief from aversive effects of nicotine abstinence increases the probability of future smoking when experiencing abstinence effects). Thus, these responses in chronic smokers are not simply the acute effects of smoking or nicotine but rather their effects in reversing the deficits in function resulting from smoking abstinence. (For simplicity, “smoking” and “nicotine” are used largely interchangeably here unless a study specifically examined only one.)

Therefore, an important issue in interpreting all research on nicotine’s effects on functioning in chronic smokers is to determine whether the effects reflect a reversal of abstinence-induced deficits in function or whether direct pharmacological changes are unrelated to the abstinence state of the subject (i.e., do not depend on abstinence-induced deficits in function). Practically speaking, this issue depends on whether the prenicotine baseline condition for a chronic smoker is (1) brief abstinence from smoking (e.g., overnight), or (2) no abstinence.<sup>175</sup> Requiring brief abstinence from smoking prevents the influence of acute tolerance to nicotine from distorting responses to subsequent smoking or nicotine administration.<sup>176</sup> However, such abstinence can also lead to mild withdrawal symptoms, including the deficits in function noted above. In this case, measures

following acute nicotine administration may reflect a reversal of these withdrawal-related deficits rather than direct effects of nicotine. This interpretation is supported by the general absence of many effects of nicotine in drug-naïve individuals who do not experience withdrawal (i.e., nonsmokers) and the attenuated effect of nicotine in smokers who are not abstinent at baseline (and not in withdrawal).<sup>177</sup>

Neither procedure—brief abstinence or no abstinence from smoking before the administration of nicotine or smoking—is necessarily superior to the other; the choice of procedure depends on the goal of the research. However, the baseline state of the smoker must be considered in interpreting results of nicotine effects.<sup>178</sup> Related to this issue is research on nicotine's effects in smokers who exhibit deficits in function from causes other than tobacco abstinence. As will be noted, nicotine can reverse many of these deficits as well as those due to ADHD symptoms, fatigue, or disease such as Alzheimer's, even when no effects are seen in smokers without these conditions. Therefore, the subject sample and session procedures need to be taken into consideration when interpreting nicotine's effects on function.

The following types of potential endophenotype measures will be considered in this section, both from the perspective of measuring nicotine effects (in a nondeprived state) as well as effects of nicotine deprivation: (1) sensory processing, (2) cognitive function, (3) craving, (4) affective regulation, and (5) behavioral regulation (impulse control). As explained, craving is included as a separate subarea because it is believed to comprise several of these functions, particularly cognitive and affective regulation, and has historically been a key concept in understanding dependence.<sup>179</sup> As in the above sections, a review is given for each measure of what is known concerning the biological

plausibility, measurement, evidence for heritability and specific genetic associations, and relationship to nicotine dependence.

## Electrophysiological Measures

### *Resting EEG Activity*

Electrical brain waves (EEG signals) can be measured to monitor changes in the brain's activity by using electrodes placed on multiple scalp locations. The spectrum of EEG activity is summarized in terms of the peak amplitude or power (area under the curve) or frequency (rate of oscillation), and is categorized into four broad frequency bands. From fastest to slowest, these include beta (13–25 hertz [Hz]), alpha (8–12.5 Hz), theta (4–7.5), and delta (1.5–3.5). The power and frequency of these EEG oscillations reflect generalized neural activity in the cerebral cortex. This activity, in turn, reflects overall level of arousal and information processing. The arousal-enhancing effects of psychostimulant drugs, including nicotine, are believed to be important to explaining their abuse liability. Therefore, nicotine's effects on EEG activation provide a potential endophenotype for dependence; however, the links of such measures to dependence are not known.

### **Biological Plausibility**

***Preclinical Research.*** The effects of acute and chronic nicotine treatment on cortical EEG activity have been assessed in Wistar rats.<sup>180</sup> Acute doses of 0.3, 0.9, and 2.7 mg/kg nicotine tartrate decreased high-voltage spindles. The effect was blocked by the nAChR antagonist mecamylamine, and when administered alone, mecamylamine increased high-voltage spindles. To test if tolerance would develop for the effects of nicotine on EEG activity, rats were chronically treated with three daily injections of 0.9 mg/kg nicotine tartrate for 10 days. No tolerance was seen for the effects of 0.9 or 2.7 mg/kg nicotine tartrate on EEG activity. In nucleus-basalis-lesioned

rats, nicotine did not alter EEG activity. The authors conclude that both acute and chronic nicotine treatment desynchronizes EEG activity. Thus, the effects of nicotine on EEG activity appear to be dependent on nucleus basalis function.

**Human Clinical Research.** In humans, nicotine causes EEG activation, as evidenced by increases in alpha and beta frequency and decreases in theta and delta power, providing a neural correlate of nicotine's arousing effects.<sup>181</sup> Abstinence from nicotine in chronic smokers produces decreases in alpha and beta frequency and increases slow wave activity; however, there is significant variability in the pattern and time course of such effects.<sup>182–185</sup> The slowing of EEG activation during nicotine abstinence in chronic smokers is associated with decrements in performance on neurocognitive tasks.<sup>183</sup>

The effects of tobacco abstinence on resting EEG can be prevented by nicotine replacement with nicotine gum or transdermal nicotine.<sup>183,184</sup> Smoking a cigarette after a brief abstinence period can reverse the decremental effects of nicotine abstinence on resting EEG<sup>182</sup> as does nicotine administration.<sup>186</sup> Further, nicotine abstinence effects on resting EEG can be mimicked by mecamylamine, an antagonist of brain nicotine receptors.<sup>187</sup> Mecamylamine pretreatment also blocks EEG effects of nicotine, suggesting that EEG neural correlates of nicotine abstinence effects are mediated by nicotinic cholinergic receptors.<sup>187</sup> The central role of nicotine, rather than tobacco more generally, is supported by the failure of denicotinized cigarettes to produce the same changes in EEG activity as nicotine cigarettes; however, nonnicotine factors may also alter EEGs.<sup>188</sup>

### **Description of Measurement of Resting EEG**

EEGs are measured by using electrodes placed on multiple scalp locations. The

assessment, analysis, and interpretation of EEG data are quite complex and beyond the scope of this chapter. Readers interested in designing EEG experiments are referred to an excellent introduction to EEG methods and measurement by Luck.<sup>189</sup>

### **Genetic Influences on Resting EEG in Humans**

Measures of resting EEG are highly stable over long periods of time,<sup>190,191</sup> suggesting that this trait is heritable. For absolute EEG power (across the EEG spectrum), heritability estimates from twin studies range from 55% to 90% in child twin pairs<sup>192</sup> and from 70% to 90% in adults.<sup>193</sup> Among a sample of 760 young adults from the Dutch twin registry, heritability estimates for the different EEG power bands were beta (.79), alpha (.90), theta (.85) and delta (.62); among middle-aged adults, estimates were similar: beta (.75), alpha (.85), theta (.75) and delta (.53).<sup>194</sup> In a review of 10 twin studies measuring alpha power, the average heritability was reported to be 79%.<sup>195</sup> The relatively lower estimates for heritability of delta wave activity suggest that environmental influences may play a more important role.

Although data from twin studies support the premise that resting, or background, EEG measures have a strong genetic basis, no studies were found of the heritability of chronic nicotine effects on EEG measures. Despite the strong evidence for the heritability of resting EEG measures, the literature on candidate gene associations is also scant. Only one genetic study was found of resting EEG components in smokers. Gilbert and colleagues followed 67 female smokers during 31 days of abstinence.<sup>196</sup> Individuals carrying the minor (*\*A1*) allele for the *DRD2\*TAQIA* polymorphism, associated with decreased D2 receptor availability,<sup>197</sup> showed significantly greater EEG slowing during a high-stress task. Similar effects were found among subjects with higher levels of nicotine dependence. This study provides the first

evidence for a genetic association with EEG measures and also suggests a link of this endophenotype with nicotine dependence.

A series of studies has been conducted in a large sample of members of families with dense histories of alcoholism.<sup>198</sup> These studies may be relevant, given the high rate of comorbidity between alcohol and nicotine dependence.<sup>91</sup> Alcohol-dependent males had significantly higher beta and theta EEG power compared to controls.<sup>199,200</sup> Genetic marker alleles across the genome were examined in these subjects, and evidence for linkage for the beta power endophenotype was found on a region on chromosome 4 that harbors the *GABA<sub>A</sub>* receptor gene.<sup>198</sup> Another investigation found a genetic association of resting EEG with a substitution polymorphism in exon 7 of the *GABA<sub>B</sub>* receptor gene, but only in normal subjects, and not in alcoholics.<sup>201</sup>

### Association of Resting EEG with Dependence

No published studies were found that relate resting EEG measures to quitting success. The study described above by Gilbert and colleagues<sup>196</sup> reported a correlation between Fagerström tolerance scores and EEG slowing at day three of nicotine abstinence; however, the relationship of these changes to quitting success is unknown. To determine the potential utility of resting EEG as an endophenotype, this critical gap in knowledge must be addressed.

## Event-Related Potentials

### General Description of ERP and Measurement

ERPs are positive and negative EEG voltage deflections in response to specific stimuli, including visual, auditory, or somatosensory.<sup>189</sup> These positive- and negative-voltage fluctuations in the amplitude of electrical activity are labeled according to their direction (P for positive, N for negative) and time (or latency) following presentation of a discrete

stimulus. ERPs are also categorized as either exogenous or endogenous. Exogenous ERPs are early deflections linked to the features of the stimulus, such as intensity of the visual or auditory stimulus. For example, the P50 ERP is an exogenous ERP observed as a positive increase in amplitude occurring at about 50 milliseconds (ms) following stimulus presentation. Exogenous ERPs, such as P50, are thought to reflect initial sensory registration. By contrast, endogenous ERPs have a longer latency, following stimulus onset, and reflect stimulus processing and evaluation. For example, the P300 ERP occurs in response to an infrequent presentation of an irrelevant stimulus, typically measured during a target detection task.

Common ERP measures include P50, N100, N200, and P300 as well as contingent negative variation and mismatch negativity. P50 and P300 have been studied most frequently in tobacco research and will be the focus here (for an in-depth review on nicotine effects on ERPs, see Pritchard and colleagues<sup>202</sup>).

### P50 ERP

#### Biological Plausibility

**Preclinical Research.** In the mouse model, the P50 ERP is measured with a paired click paradigm but has a shorter latency (20 ms). In rodents, it is therefore referred to as the P20-N40 wave. DBA/2 mice have a deficit in auditory gating of the P20-N40 wave, and nicotine reverses this deficit.<sup>203,204</sup> Acute nicotine also increases the amplitude of the P20 wave and decreases the amplitude of the N40 wave in C57BL/6J mice and DBA/2Hsd mice.<sup>205</sup>

There is evidence from rodent models for  $\alpha 7$  nAChR involvement in P20-N40 amplitude and P20-N20 gating.<sup>206</sup> Nine strains of inbred mice were analyzed for  $\alpha$ -bungarotoxin binding (a ligand for  $\alpha 7$  nAChR) and P20-N40 gating. A significant correlation was observed



between hippocampal  $\alpha$ -bungarotoxin binding and the P20-N40 response to the first auditory stimulus and the ratio of response to the first and second stimulus (i.e., the gating response). Nicotine has been shown to increase P20 and reduce N40 amplitude. These effects are sensitive to manipulation of dopamine.<sup>207</sup> Mecamylamine attenuates nicotine effects on P20, but not on N40, suggesting a different role for nAChRs in these response waves.<sup>208</sup>

**Human Clinical Research.** Much of what is known about the P50 has come from research in the area of schizophrenia that focuses on a common P50 sensory gating deficit. Some studies suggest that schizophrenic patients exhibit a reduced ability to inhibit, or complete failure to inhibit, a brain response to the second of two auditory stimuli (see below).<sup>209,210</sup> Smoking prevalence rates are as high as 80% among individuals with schizophrenia, significantly higher than in the general population.<sup>211</sup> It has been posited that these elevated smoking rates are partly due to a normalizing effect of nicotine on the P50 response.<sup>212,213</sup> Therefore, the literature on genetic associations with the P50 response in schizophrenia, discussed below, may help to elucidate the possible use of this measure as an endophenotype of nicotine dependence.

### Description of Measurement of P50 ERP in Humans

As mentioned above, the P50 ERP is a positive EEG voltage deflection that occurs about 50 ms after presentation of an auditory or visual stimulus, and it reflects initial sensory registration. Much of this research in humans focuses on the P50 sensory gating deficit. This is typically measured in a paired-stimulus paradigm in which two stimuli (usually a sound or a “click”) are presented about 5 ms apart. The ratio of response to the second stimulus versus the first stimulus is averaged over a large number of trials in this paradigm. In normal subjects, there is an average reduction in the response to

the second stimulus, reflecting an adaptive sensory gating or filtering mechanism.

### Genetic Influences on the P50 ERP in Humans

Existing evidence suggests that the P50 ERP has a substantial genetic component. In healthy twins, heritability estimates for the P50 sensory gating response range from .44 to .68 for this measure.<sup>195,214,215</sup> Given the evidence for genetic influences, it is not surprising that the measure is fairly stable over time; interclass correlations of .66–.77 have been reported for P50 suppression, when measured on two separate occasions.<sup>216</sup> Interestingly, there is not strong evidence for significant shared genetic influences with the P300, suggesting different neurobiological mechanisms for P50 and P300.

Work on the specific genetic basis of the P50 ERP has focused on the P50 suppression deficit seen in schizophrenics. Consistent with evidence for the central role of the  $\alpha 7$  nAChR cited above, a genome-wide analysis found evidence for significant linkage of the P50 auditory to a region in chromosome 15 that includes the  $\alpha 7$  nicotinic receptor gene *CHRNA7*.<sup>217</sup> Subsequently, Leonard and colleagues identified polymorphisms in the promoter region of *CHRNA7* with reduced transcriptional activity in reporter gene assay.<sup>218</sup> In this study, schizophrenic patients exhibited less P50 inhibition than did controls, and a functional *CHRNA7* polymorphism was associated with this measure.<sup>218</sup> Although schizophrenia has been linked to this region and associated with *CHRNA7*,<sup>218</sup> another group was unable to replicate the associations of the promoter variants with the P50 gating deficit.<sup>219</sup>

### Association of P50 ERP with Nicotine Dependence

No published studies were found of the relationship of the P50 ERP or P50 suppression with level of nicotine dependence or quitting success.



## **P300 ERP**

### **Biological Plausibility**

There has been little attention to effects of nicotine on the P300 in animal models. In one study, prenatal nicotine exposure in rats predicted a reduced auditory P300 ERP in the adult offspring relative to controls.<sup>220</sup>

In humans, differences between smokers and nonsmokers in the P300 ERP have been documented in a few studies.<sup>221,222</sup> Both current and former smokers show reduced P300 amplitude that correlates with hypoactivation in the anterior cingulate and frontal cortical regions.<sup>223</sup> The presence of the deficit in former smokers suggests that this may be a predisposing factor rather than a consequence of nicotine exposure. However, it is also possible that both current and former smokers have neuroadaptive changes due to chronic nicotine exposure that are not reversed following long-term cessation.

Of greater relevance to withdrawal-related phenotypes are studies examining effects of tobacco abstinence on the P300 ERP. Brief abstinence from tobacco increases P300 latency and decreases P300 amplitude, effects that are reversed by smoking.<sup>181</sup> In one study of smokers abstaining for nine hours, smoking two cigarettes reduced P300 amplitude.<sup>224</sup> However, another study found that 12-hour abstinence had no effects on P300 amplitude but did increase P300 latency.<sup>225</sup> Although the results of investigations of effects of nicotine and of tobacco abstinence on P300 are not entirely consistent, there is some evidence suggesting that P300 deficits may predispose to smoking, are intensified by abstinence in chronic smokers, and are reversed by smoking following brief abstinence.

### **Description of Measurement of P300 ERPs in Humans**

As mentioned above, the P300 is an endogenous, positive EEG deflection at

about 300 ms following a stimulus. Unlike the P50 ERP, which is a purely sensory response, the P300 is sensitive to differences in stimulus parameters. It is typically measured in a visual or auditory oddball paradigm in response to an infrequent (i.e., “oddball”) stimulus occurring in the context of common target and nontarget stimuli in a target-detection task.

Generally speaking, the more unexpected and infrequent the oddball stimulus, the stronger is the ERP response. The P300 is measured across a large number of trials and reported in terms of both average peak amplitude and average latency from the stimulus, with the former reflecting the amount of cognitive resources required for stimulus processing and evaluation and the latter reflecting the time required for such processing.<sup>202</sup>

### **Genetic Influences on the P300**

In general, P300 amplitude and latency appear to be stable and heritable traits. Test-retest correlations of .66–.67 are reported for assessments performed on two separate occasions.<sup>214</sup> In adolescents, test-retest correlations are also high.<sup>226</sup> The strongest evidence for the heritability of the P300 ERP is presented in a meta-analysis of five twin studies, reporting a “meta-heritability” of 60% (95% confidence interval [CI], 54%–65%) for P300 amplitude and 51% (95% CI, 43%–58%) for P300 latency.<sup>195</sup> In individual twin studies, heritability estimates for P300 amplitude and latency range from .41 to .78.<sup>214,227,228</sup> Although P300 amplitude and latency share genetic variance (i.e., one-half of the variance in these measures is due to common genetic influences), there is no evidence for significant shared genetic influences for the P300 and P50 ERP, suggesting different neurobiological mechanisms.<sup>216</sup> No studies were identified of genetic influences on effects of nicotine or tobacco abstinence on the P300; however, given consistent evidence that the trait itself is heritable, genetic variation in nicotine effects would be expected.

Genetic association studies of P300 focusing on effects of nicotine or smoking are rare. However, there is growing evidence for specific genetic influences on the P300 in the general population and in populations in which smoking rates are high. For example, using genome-wide linkage analysis in the Collaborative Study on the Genetics of Alcoholism, Porjesz and colleagues<sup>198</sup> found evidence for linkage of P300 (measured in a visual task) to regions on chromosomes 2, 5, 6, and 3.

Evidence for genetic linkage supports the pursuit of specific genes that may underlie deficits in P300 that may have relevance to nicotine dependence. Given the importance of dopamine signaling in schizophrenia, polymorphisms in genes in the dopamine pathway have been examined for associations with P300, although with mixed results. The *DRD2\*TAQ1 A1* variant, associated with smoking risk in some studies, has also been linked with prolonged P3 latency in the sons of active and recovering alcoholics.<sup>229</sup> A nonsynonymous (*SER9GLY*) variant in the dopamine receptor D3 gene (*DRD3*) previously associated with schizophrenia has been related to reduced P300 amplitudes in the left parietal area.<sup>230</sup> The reduced activity \*7-repeat allele of a common dopamine receptor D4 VNTR polymorphism has been linked with P300 response to novel stimuli; the results, however, were modified by a measure of dopaminergic tone (i.e., the eyeblink response).<sup>231</sup> Although these studies have not focused specifically on nicotine effects, both the *DRD2\*TAQ1 A1* and the *DRD4\*7-repeat* allele have been associated with smoking status in some studies,<sup>31,38</sup> and *DRD3* activity mediates, in part, nicotine self-administration in rodent models.<sup>232</sup>

As discussed further below with respect to neurocognitive deficits, the *COMT* gene is an excellent candidate gene for measures involving sensory processing and neurocognitive function. The COMT enzyme inactivates dopamine, with important effects

in the prefrontal cortex where dopamine transporter (reuptake) levels are low.<sup>233</sup> Among schizophrenics, carriers of the low-activity \**MET* allele (increased dopamine) show smaller frontal P300 amplitudes, an effect interpreted as reflecting less “noise” in the prefrontal cortex.<sup>234</sup> During a task of behavioral inhibition mediated by the frontal cortex (i.e., go/no-go) *COMT\*MET* allele carriers show an anteriorization of the P300 response during the no-go target, which the authors suggest may alter ability to inhibit responses.<sup>235</sup> However, other studies have found no association of *COMT* genetic variation with P300 amplitude or latency.<sup>236</sup> No studies were found examining the role of genetic factors on nicotine effects on the P300.

### Association of P300 ERP with Nicotine Dependence

As with the P50 ERP, no published studies were found of the relationship of the P300 ERP with level of nicotine dependence or quitting success.

### The PPI of Startle Response

The PPI of the acoustic startle reflex is another task thought to measure the ability to filter sensory information or sensory gate.<sup>237,238</sup> Although the basic construct involving inhibition or “gating” of response to a second stimulus is similar to the P50 ERP, this measure is based on an eyeblink reflexive response, rather than on electrophysiological measurement (discussed below).

### Biological Plausibility

The effects of acute nicotine on PPI across strains of mice and rats are highly variable, supporting genetic influences. In one study, acute nicotine administration enhanced PPI in C57BL/6 mice.<sup>239</sup> In a strain survey of the effects of nicotine on PPI in 129S6, BALB/cByJ, C57BL/6J, DBA/2, and NMR1 mice, nicotine enhanced PPI only in NMR1 mice.<sup>240</sup> Another study

found no enhancement of PPI with nicotine in DBA/2J, C3H/HeJ, C57BL/6, or 129T2/SvEmsJ mice.<sup>241</sup> The different effects of nicotine on PPI may be due to different doses of nicotine used and to strain differences. The study by Spielow and Markou<sup>241</sup> found genetic differences in the ability of nicotine to reverse phencyclidine (PCP) disruption of PPI; nicotine reversed PCP-associated deficits in PPI in DBA/2J and C3H/HeJ mice but not in C57BL/6 or 129T2/SvEmsJ mice. In Sprague-Dawley rats,<sup>242,243</sup> nicotine enhanced PPI, but in Wistar rats, nicotine had no effect on PPI.<sup>244</sup> In a study that compared the effects of nicotine on PPI between Sprague-Dawley rats and BALB/c mice, nicotine disrupted PPI in the Sprague-Dawley rats but enhanced PPI in the BALB/c mice.<sup>245</sup> In  $\alpha 7$  nAChR subunit knockout mice, no deficits in PPI were found.<sup>246</sup> However, PPI was disrupted in  $\beta 3$  nAChR knockout mice, suggesting that  $\beta 3$ -containing nAChRs are involved in PPI.<sup>247</sup>

With respect to preclinical studies of nicotine withdrawal effects on PPI, DBA/2 mice withdrawn from nicotine showed decreased PPI for the 8-decibel (dB) and 12-dB prepulses but not for the 4-dB prepulse.<sup>248</sup> A follow-up study from the same laboratory compared the effects of nicotine withdrawal on PPI in DBA/2 mice and C57BL/6 mice and found no withdrawal-associated PPI deficits.<sup>249</sup> The different results across studies could be related to the different doses used or could suggest that the effects of nicotine withdrawal on PPI are mild. In support of the latter, no nicotine withdrawal deficits were seen in PPI in Long-Evans rats, Sprague-Dawley rats, and Wistar rats.<sup>237,250</sup>

In humans, acute smoking of a cigarette has been shown to increase PPI (i.e., reverse the attenuation due to abstinence) very acutely within minutes after smoking.<sup>251,252</sup> Demonstration that a subcutaneous injection of nicotine (6 or 12  $\mu\text{g/kg}$ ) also increased PPI confirmed that nicotine

per se increases PPI.<sup>253</sup> In contrast, PPI is attenuated (i.e., less inhibition of startle or sensory gating) by overnight abstinence in dependent smokers.<sup>252</sup> Thus, while there has been less attention to nicotine's effects on PPI, as compared with EEG measures, these data suggest that PPI could be a plausible endophenotype.

### Description of PPI Measurement in Humans

PPI is typically measured within a classic startle paradigm that assesses reflexive muscle contractions by using electromyographic, or EMG, recording of the orbicularis oculi muscles (eyeblink response) following presentation of a sudden intense stimulus (visual, auditory, or tactile). The startle reflex itself is thought to relate to mood or affect and is discussed later in this chapter as a potential endophenotype of affect regulation. PPI of the startle response reflects the extent to which a preceding weaker stimulus suppresses or attenuates the sensorimotor reflex response to the subsequent intense stimulus. This response occurs in animals and humans, although there is substantial individual variability.<sup>254</sup> Various adaptations of this paradigm have used pictorial representations of smoking cues or affective stimuli; however, using smoking cues as the prestimulus does not appear to modulate the acoustic startle response.<sup>255</sup>

### Genetic Influences on Prepulse Inhibition of Startle

Although there is evidence for high retest reliability for PPI measures, suggesting that this is a stable trait measure,<sup>256,257</sup> only one study has examined the heritability of PPI. In this study of 170 female twins aged 18–28 years, it was estimated that roughly 50% of the genetic variability in PPI is due to genetic influences, some of which are shared with absolute startle response.<sup>258</sup> However, a follow-up study of affective modulation of startle provided no evidence for significant heritability.<sup>259</sup> At the writing of this chapter, no studies

were identified relating specific genetic variants to PPI.

### **Association of PPI with Nicotine Dependence**

Of these EEG measures, only PPI has been studied in relation to cessation outcome or other indices of nicotine dependence. In the study by Kumari and colleagues<sup>252</sup> described above, PPI was attenuated (i.e., less inhibition of startle or sensory gating) by overnight abstinence to a greater degree in more dependent smokers, based on their score on the Fagerström Tolerance Questionnaire. This suggests that attenuation in PPI due to overnight abstinence relates cross-sectionally to degree of current dependence on one self-report measure of dependence.

## **Cognitive Function**

### ***Attention and Vigilance***

#### **Biological Plausibility**

Nicotine's effects on attention have been the focus of several studies in rodents. The five-choice serial reaction time task (5CSRTT) is one of the best studied of these models. In the 5CSRTT, rodents must attend to an array of five apertures for presentation of a brief light stimulus and respond with a nose poke in the illuminated aperture for food reinforcement. The 5CSRTT allows for assessment of multiple behavioral measures that include the percentage of correct responses (i.e., accuracy), percentage of omissions (i.e., the failure to respond to the stimulus), response latency, latency to collect the reinforcement, and premature responding (i.e., nose pokes during the intertrial interval); for a review, see Kumari and colleagues.<sup>260</sup>

Several studies have used the 5CSRTT to study nicotine effects on attentional processes. Acute nicotine enhances attention in the 5CSRTT, increases reaction time on correct responses, and increases accuracy.<sup>261–263</sup> Surprisingly few animal

studies have examined the effects of nicotine withdrawal on attentional processes. In one study, hooded Lister rats were tested for the effects of withdrawal from 3.16 mg/kg/day of nicotine on the 5CSRTT.<sup>264</sup> Increased omissions were seen after both spontaneous withdrawal and precipitated withdrawal with the high-affinity nAChR antagonist DH $\beta$ E; the  $\alpha$ 7 nAChR antagonist methyllycaconitine did not precipitate withdrawal. Thus, nicotine withdrawal was associated with an increased failure to respond to the stimuli. This deficit in attention to the stimuli involves high-affinity nAChRs such as the  $\alpha$ 4 $\beta$ 2 nAChR.

An alternate paradigm for assessing nicotine's cognitive effects in rodents is fear conditioning (in which a neutral stimulus is paired with an aversive stimulus, and then freezing to the neutral stimulus is measured). In one study,<sup>265</sup> C57BL/6 mice were treated with nicotine for 12 days and then withdrawn from nicotine; 24 hours later, mice were conditioned. Nicotine withdrawal disrupted contextual fear conditioning, a hippocampus-dependent version of fear conditioning,<sup>266,267</sup> but not cued fear conditioning, a hippocampus-independent version of fear conditioning.<sup>266,267</sup> The selectivity of the withdrawal deficits suggests that nicotine withdrawal affects specific types of learning and does not affect processes common to both types of learning. It is possible that relapse occurs in smokers after withdrawal from nicotine as an attempt to ameliorate learning-related deficits. In support, the withdrawal deficit in contextual fear conditioning in mice was reversed by treatment with acute nicotine.<sup>265</sup>

Animal studies examining the genetic basis of nicotine effects on attention are limited, but the effects of nicotine on five-choice serial reaction time (5CSRT) have been shown to be strain dependent in rats. Nicotine improved choice accuracy in Sprague-Dawley rats but not in hooded

Lister rats.<sup>268</sup> Another study demonstrated that nicotine enhanced 5CSRT in C57BL/6 mice.<sup>269</sup> In this study, drug-naïve  $\alpha 7$  nAChR subunit knockout mice showed deficits in 5CSRT, compared to wild-type mice. Thus,  $\alpha 7$  nAChR may be involved in some attention processes.

In humans, several converging lines of evidence have linked self-reported inattention symptoms to smoking behavior. Individuals with a clinical diagnosis of ADHD have higher rates of smoking initiation and persistence. Further, smokers with a history of ADHD (current or childhood) are more likely than those without a history of ADHD to experience nicotine withdrawal symptoms, including irritability and problems with concentration.<sup>270</sup> Inattention symptoms are also associated with self-reported reasons for smoking (e.g., smoking for stimulation) and nicotine dependence in the general population of smokers.<sup>271</sup> Impulsivity symptoms are also associated with smoking prevalence in young adults.<sup>272</sup> Most critically, smokers without a diagnosis of ADHD who reported increases in subclinical ADHD symptoms during the first week of abstinence were significantly more likely to relapse than were smokers who did not report increases in inattention symptoms.<sup>273</sup> Improvements in attention and performance due to nicotine have also been reported in studies of nonsmokers without ADHD<sup>274</sup> and smokers and nonsmokers with ADHD.<sup>275</sup>

### Description of Measures of Attention and Vigilance in Humans

Measures of attention tap the ability to focus and sustain attention on relevant stimuli. The most commonly used measure of visual attention is the continuous performance task (CPT). In this computerized task, participants are presented with a visual target for 50 ms (e.g., an “X”) and nontarget stimuli (e.g., an “O”) in rapid succession. They are instructed to make a rapid response (e.g., press a button) only when a target

stimulus is presented. A variation on the basic CPT (CPT-identical pairs [IP]) is to instruct participants to make a response when they see an identical pair of targets (e.g., two digits or letters) presented in succession.<sup>276</sup> CPT-IP has been advocated for use in adults, as the basic CPT may not be sensitive enough to capture inattention symptoms in the general population.<sup>277,278</sup> The CPT has been shown to discriminate between those with and without ADHD among children and adults<sup>279–281</sup> and to be sensitive to the effects of ADHD medications.<sup>282</sup> As described above, the CPT is sensitive to the effects of nicotine abstinence<sup>282</sup> and nicotine administration.<sup>275</sup>

Other measures of visual attention that are sensitive to nicotine effects include the Rapid Visual Information Processing (RVIP) task<sup>283</sup> and the letter cancellation task.<sup>284</sup> Regular smokers observed over 24 hours of abstinence performed more poorly on this cancellation task, with reduced rates of target detection and increased response times as duration of abstinence increased, demonstrating withdrawal-induced deficits. Finally, auditory attention can be measured with the Digit Span test of the Wechsler Adult Intelligence Test-Revised, which is sensitive to medication effects,<sup>285</sup> but not well studied with respect to nicotine effects. In general, most studies show that smoking, or nicotine delivery by other methods in abstinent smokers, produces only modest improvements in simple reaction time performance, finger-tapping speed over short periods (e.g., less than one minute), or other simple psychomotor tasks.<sup>177</sup>

### Genetic Influences on Attention and Vigilance

Although no studies were found that examined the heritability of nicotine-related effects on measures of attention and vigilance, existing data support the heritability of baseline task performance.<sup>286</sup> For the CPT, heritability estimates of 39% and 49% have been reported for verbal



and spatial attention, respectively.<sup>276</sup> For the digit symbol substitution test, heritability estimates of 67% have been reported.<sup>287</sup> By using a simple reaction time task in a sample of 213 twins, the heritability of attentional/motor performance was estimated to be 64%. Other studies have focused on the heritability of performance within families with schizophrenia. For example, using a registry of families with schizophrenia in Finland, Tuulio-Henriksson and colleagues,<sup>288</sup> reported heritabilities of .09 and .20 for visual and auditory attention, respectively. Thus, while there is general support for the heritability of performance of tasks assessing attention, the genetic contributions appear to vary by both measure and population.

Associations of candidate genes in the dopamine pathway with attention-vigilance measures have also been reported; however, the results have not been consistent. In the single study of genetic associations with nicotine effects on attention, Gilbert and colleagues found that smokers carrying the “high-risk” *\*AI* allele of the *\*TAQI* polymorphism in the *DRD2* gene exhibited greater improvements in RVIP task performance following nicotine administration.<sup>289</sup> Several studies have examined the *VAL/MET* polymorphism in the *COMT* gene described above. Consistent with the premise that dopamine levels in prefrontal cortex facilitate attention, the low-activity *\*MET* allele has been associated with better performance on the CPT;<sup>290,291</sup> however, another study found no association between CPT performance and the *COMT* genotype.<sup>292</sup> Performance on the CPT has also been associated with a common repeat polymorphism in the dopamine transporter gene among children with ADHD; however, the direction of association is inconsistent across studies.<sup>293,294</sup> One study provides evidence for an association of a repeat polymorphism in the dopamine receptor D5 gene *DRD5* with CPT performance in children with

ADHD and their parents.<sup>295</sup> Visuospatial attention has also been associated with a polymorphism in the  $\alpha 4$  nicotinic receptor gene *CHRNA4*, providing further support for attention-related endophenotypes of nicotine dependence.<sup>296</sup> Thus, although only one study examined the role of specific genetic factors in nicotine effects on attention,<sup>289</sup> the genetic associations identified for task performance (independent of nicotine) are consistent with those found for smoking status and smoking cessation.

### Relation of Attention and Vigilance Measures to Dependence

Several of the measures described above are sensitive to effects of nicotine deprivation in dependent smokers.<sup>297,298</sup> In addition, smokers with higher scores on the FTND exhibit increased neural activation in regions related to visuospatial attention (e.g., anterior cingulate cortex) while viewing smoking and neutral pictures,<sup>299</sup> suggesting that nicotine dependence may moderate attentional task performance.

Two small studies assessed relationships of CPT to quitting success. In one study of adolescent smokers, commission errors on the CPT predicted relapse;<sup>300</sup> however, commission errors may be more reflective of impulse control deficits than attention-vigilance (see section below on “Impulse Control”). In a study of schizophrenic smokers, baseline CPT performance did not predict quitting in a smoking treatment program.<sup>301</sup>

### Working Memory

#### Biological Plausibility

Nicotine’s effects on learning are a plausible mechanism for its positive and negative reinforcing effects.<sup>302</sup> For example, learned associations of nicotine delivery with smoking-related stimuli may promote drug craving. Likewise, the ability of nicotine to reverse cognitive deficits could contribute to relapse if abstinent smokers attempt



to ameliorate the withdrawal deficits by resuming smoking.

This premise has received substantial support in rodent models of nicotine's effects on learning. Specifically, nicotine enhances hippocampus-dependent contextual fear conditioning,<sup>265,303–306</sup> it does not enhance the hippocampus-independent association between the auditory conditioned stimulus (CS) and the foot shock unconditioned stimulus (US),<sup>305,306</sup> even when the difficulty of the task is increased.<sup>307</sup> Acute nicotine has also repeatedly been shown to enhance working memory, as measured in the 8-arm radial maze (for a review see Levin and Simon<sup>308</sup>) and as measured in trace fear conditioning.<sup>307,309</sup> Nicotine also improves learning in paradigms such as passive avoidance,<sup>310–312</sup> active avoidance,<sup>313,314</sup> the Morris water maze,<sup>315,316</sup> and a visual discrimination task.<sup>317</sup>

With respect to the genetic underpinnings of nicotine's effects on learning, the earliest studies focused on strain surveys of inbred mice. In work by Bovet and colleagues,<sup>318</sup> nicotine produced the most active avoidance in C3H/He mice followed by CBA mice, C57BL/6 mice, AHe mice, Swiss mice, BALB/c mice, and then DBA/2 mice. In the remaining strains, nicotine disrupted learning, with the greatest deficit seen in C57BR/cd mice followed by C57BL/10 mice, and then A/J mice. In a visual discrimination task in which mice learned to exit a chamber through the correct door to avoid a shock, nicotine enhancement of learning varied across inbred strains of mice.<sup>319</sup> In A/J, C3H/He, and DBA/2J mice, nicotine enhanced visual discrimination (C3H/He  $\geq$  DBA/2J  $\geq$  A/J), but in the BALB/c strain, nicotine disrupted performance. In a comparison of the effects of nicotine on consolidation of a Y-water-maze task, nicotine improved consolidation in C57BL/6 mice but disrupted consolidation in DBA/2 mice.<sup>320</sup> Thus, comparisons across inbred strains of mice show clear influences of

genetics on the acute effects of nicotine on learning and also suggest that these effects may be task specific.

Targeted mutations and selective breeding studies also support the influence of genetic factors in the effects of nicotine on cognition. No deficits in either passive avoidance or fear conditioning were seen in  $\beta 2$  nAChR subunit knockout mice;<sup>321,322</sup> nicotine, however, failed to enhance passive avoidance and contextual fear conditioning in the  $\beta 2$  knockout mice.<sup>322,323</sup> In contrast to the  $\beta 2$  knockout mice, nicotine enhanced contextual fear conditioning in  $\alpha 7$ ,  $\beta 3$ , and  $\beta 4$  nAChR subunit knockout mice.<sup>323</sup>

Studies with nAChR knockout mice also suggest that the  $\beta 2$  nAChR subunit is involved in the effects of nicotine on working memory. Working memory is defined as the processes by which information is maintained for access while performing complex cognitive tasks. One measure of working memory is trace fear conditioning in which the CS and the US are separated by a trace period during which no stimulus is presented; therefore, a representation of the CS must be maintained during the trace period for a CS-US association to be learned.<sup>324–326</sup> Both  $\beta 2$  and  $\alpha 7$  nAChR subunit mice develop trace fear conditioning, but in the  $\beta 2$  knockout mice, nicotine does not enhance conditioning.<sup>309</sup> Together, these results suggest that genetic alterations of the  $\beta 2$  subunit gene alter the effects of nicotine on multiple types of learning.

The human data on nicotine's effects on working memory are less clear. There is evidence for enhancement of working memory following acute nicotine delivery in nonsmokers.<sup>260</sup> However, nicotine gum does not improve working memory in nonsmokers.<sup>327</sup> The nicotine patch (six hours) enhances working memory only in a subgroup of individuals characterized as "highly attentive."<sup>328</sup> In chronic smokers,

acute nicotine delivered via nasal spray appears to have no effect on verbal working memory, but may have small effects on spatial working memory.<sup>329</sup>

Nicotine deprivation in chronic smokers appears to produce decrements on working memory tests. Adolescent smokers deprived of nicotine for 24 hours exhibit significant decrements in performance on an auditory working memory task, compared to performance in a nondeprived state.<sup>330</sup> More than 13 hours of nicotine deprivation also results in longer response latency and poorer performance on an N-back task in adult smokers, compared to performance when nondeprived.<sup>331</sup> Similarly, Foulds and colleagues<sup>332</sup> found that subcutaneous nicotine injections (0.3 and 0.6 mg) in abstinent smokers produce faster reaction time on some working memory tasks (e.g., the RVIP), but decreased accuracy on others (e.g., digit recall), compared to saline injections. Abstinent smokers tended to show stronger improvements in RVIP performance due to nicotine than did a comparison group of nonsmokers, again supporting the notion that much of the performance-improving effects of nicotine may reflect reversal of deficits due to withdrawal.

In using the Sternberg memory task, one study found that nasal spray nicotine improves performance of smokers but only under conditions of auditory distraction, which caused decrements in performance at baseline, and not under normal nondistracted conditions.<sup>333</sup> Thus, effects of nicotine were seen only when the ability to perform the task was impaired because of an environmental condition (distraction), similar to other findings showing nicotine effects when performance is impaired by withdrawal. Nicotine had no effect on performance in nonsmokers, showing that chronic smoking exposure is necessary for nicotine to have any apparent beneficial effect.

### **Description of Working Memory Tasks in Humans**

Some of these tasks are described in detail in chapter 8. Others used primarily with chronic smokers are described here.

***N-Back Task.*** The N-back task, a measure of working memory, is being applied increasingly in human work on nicotine dependence.<sup>331,334</sup> In this task, participants are asked to look at flashing letters (or geometric figures) on a computer screen, one at a time, and to press the space bar according to four principles or rules: 0-back, 1-back, 2-back, and 3-back. During 0-back, the participant must press the space bar whenever the target stimulus (e.g., letter “X”) appears on the screen. During 1-back, the participant must press the space bar whenever the target stimulus is the same as the previous stimulus (i.e., the stimulus 1-back). A similar rule is followed for 2-back and 3-back, with increasing memory load from 1-back to 3-back. The primary outcomes include the percentage correct and reaction time to correct responses.

***Wisconsin Card Sorting Test.*** The Wisconsin Card Sorting Test (WCST) is a widely used measure of prefrontal cognitive function that is sensitive to a subject’s ability to generate hypotheses, establish response sets, and fluently shift sets.<sup>335</sup> Subjects are required to sort stimulus cards on the basis of perceptual attributes (color, form, number). The only feedback provided by the administrator is whether each response is correct or incorrect. The sorting rule is changed after 10 consecutive correct responses. Testing is discontinued when the subject has learned two iterations of the three sorting rules or has reached 128 trials. The primary outcomes include number of categories achieved, number of trials, number of errors, and percentage and number of perseveration errors.

***Sternberg Memory Task.*** Although not as widely used in nicotine research as

the N-back and the WCST, the Sternberg memory task is a test of verbal memory that requires subjects to memorize a string of letters during a brief (e.g., 10 seconds) period and then to recognize these letters as they are presented individually (in a set that includes letters not part of the original set). Transdermal nicotine has been shown to reverse deficits on this task produced by haloperidol administration.<sup>336</sup> Yet, at least two studies show no clear effects of nicotine via nasal spray on performance of this task in nonsmokers,<sup>333,337</sup> suggesting that effects of nicotine on such performance may depend on prenicotine level of impairment in performance.

### Genetic Influences on Working Memory

Genetic contributions to components of working memory have been explored in a couple of twin studies. For example, in a study of 236 healthy twin pairs, the heritability of working memory was found to range from 43% to 49% for verbal and spatial memory storage (with minimal difference for verbal vs. spatial).<sup>338</sup> Among healthy twins, working memory task performance ranged from 35% to 50%.<sup>339</sup> The degree of heritability of nicotine or abstinence effects on working memory is unknown.

The most widely studied genetic variant in studies of working memory is the *COMT VAL/MET* polymorphism, related to dopamine levels in the frontal cortex, a critical brain region for executive function. In studies of healthy children, adults, patients with schizophrenia, and their relatives, the high-activity *\*VAL* allele of *COMT* (lower brain dopamine levels) has been associated with poorer performance on working memory tasks (e.g., WCST, N-back).<sup>290,292,340,341</sup> Interestingly, a few of these studies assessed working memory concurrent with functional magnetic resonance imaging (fMRI). In addition to poorer task performance, several studies show increased activation in regions

of interest (e.g., dorsolateral prefrontal cortex, anterior cingulate), suggesting “less efficient processing” capacity in the *\*VAL* allele carriers.<sup>233,290,340,342,343</sup> Studies have explored associations of the functional brain-derived neurotrophic factor (BDNF) *VAL66/MET* polymorphism with working memory performance. One study reported no association in healthy adolescents,<sup>344</sup> two studies reported a positive association between the *\*VAL* allele and performance in psychiatric patients,<sup>345,346</sup> and another study reported abnormal neural activation in the hippocampus during N-back task performance in healthy adults with the BDNF *\*MET* allele.<sup>347</sup>

Only one study was found that examined the relationship of a specific genetic polymorphism with nicotine effects on working memory performance in smokers. In this study,<sup>348</sup> 36 adults (22 smokers) completed the N-back task during two fMRI sessions (one with nicotine patch, the other with placebo patch). Individuals with the *\*T* allele for the functional *DRD2 C957T* polymorphism had worse performance following nicotine administration than those with the *\*C* allele, a finding attributed by the authors to excess dopaminergic stimulation by nicotine in *\*T* allele carriers.<sup>348</sup> Consistent with other evidence described above, nicotine enhancement of performance may be more difficult to demonstrate; therefore, genetic studies of nicotine abstinence effects on working memory performance may be more informative. Another study found complex, dose-related associations between *DRD4* genotypes and acute nicotine effects on performance of the Sternberg memory task among nonsmokers,<sup>337</sup> as noted in chapter 8.

### Relation of Working Memory Measures with Dependence

Only one study was identified relating performance on a working memory task to nicotine-dependence measures or

quitting success. In this small study of schizophrenics, deficits in a visuospatial working memory task predicted a greater likelihood of relapse.<sup>301</sup>

### Craving

Craving has long been viewed as a key element of drug dependence in general,<sup>179</sup> and craving for cigarettes is a hallmark of nicotine withdrawal, along with negative mood.<sup>2</sup> Craving to smoke is thought to be sensitive to at least two broad influences: (1) recent abstinence from smoking (withdrawal) and (2) the presence of discriminative stimuli for smoking (cues). Both types of craving tap the urge to smoke, but the specific underlying mechanisms are undoubtedly different. Notably, the evidence linking each of these types of craving to dependence differs substantially. Thus, these different types of craving appear to reflect very different processes, justifying their clear distinction. The following sections distinguish between these types of craving in evaluating their potential as endophenotypes. However, the description of craving measures other than self-report will emphasize cue-induced craving; these measures are less common in studies of abstinence-induced craving.

### Biological Plausibility

#### Abstinence-Induced Craving

Dependence is marked in part by persistent drug use despite the adverse consequences, sometimes indicated by an inability to abstain. Craving, or a desire to use the drug, that emerges as a result of abstinence is one index of difficulty remaining abstinent, as greater craving is often viewed as a precipitant of relapse (failure to abstain).<sup>114</sup> Craving is very reliably increased by duration of smoking abstinence, up to a few days when it tends to peak, and nicotine treatment reliably decreases this craving.<sup>349</sup> Although drug use is not always

directly predicted by self-reported craving, particularly in smokers not trying to quit,<sup>350</sup> to some extent the biological plausibility for abstinence-induced craving being an endophenotype rests on its high face validity or the reasoning that greater self-reported desire to use the drug reflects the intention to do so.

#### Cue-Induced Craving

Because abstinence-induced craving has high face validity and has been shown to predict success of a quit attempt (see below), research has investigated the notion that very acute increases in craving elicited by smoking cues may also have predictive validity or, at least, are otherwise important to understanding nicotine dependence. The notion that much of smoking behavior is conditioned to environmental stimuli—that is, cues—has strong support in the literature. Environmental stimuli clearly become conditioned to nicotine and other drug intake in animal models, such that drug self-administration can come under the control of drug-associated cues, regardless of the presence of the drug itself.<sup>78</sup> Because smokers strongly respond to smoking cues with increases in self-reported craving, and those with very little smoking exposure history (e.g., nonsmokers) do not,<sup>351</sup> chronic exposure to smoking must condition these craving responses to cues. As further evidence of cue-induced craving, smokers have greater craving responses to environments generally associated with smoking, such as bars, but not to environments where smoking is discouraged, such as churches or theaters. Moreover, smokers respond with even more craving to environments in which they personally tend to smoke (e.g., the interior of their car or in their favorite bar) compared to environments unfamiliar to them but where other smokers tend to smoke (e.g., someone else's car or an unfamiliar bar<sup>352</sup>). No other explanation is plausible other than that these environments have come

to elicit craving because of their past association with smoking behavior by the smoker—that is, cue-induced craving. Thus, it would seem very plausible that those who report greater desire to smoke in response to smoking-associated stimuli, or representations of those stimuli (e.g., pictures), should be less likely to refrain from smoking when they confront those stimuli in their environments after quitting (and thus are more nicotine dependent).

Evidence supporting a biological basis for cue-induced craving is found in human neuroimaging research.<sup>353</sup> Experiments using fMRI and positron emission tomography (PET) have explored differences in regional brain activation during presentation of smoking and neutral cues, presented in pictorial or video format. Brain regions most commonly activated during smoking cue presentation include those important in incentive motivation, reward signal processing, and goal-directed behavior (e.g., orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate).<sup>354–357</sup> Subjective craving during cue exposure correlates with a subset of these regions, although results are not consistent across all studies. Discrepancy in findings across neuroimaging studies of cue-induced smoking craving may be attributable to individual and contextual factors that moderate these responses.<sup>358</sup> For example, increased activation is reported when individuals are told they can smoke immediately following the session.<sup>359</sup> Differences in racial background may also be important.<sup>357</sup> Of importance for the endophenotype criteria used in this chapter, brain activation in response to smoking cues has also been associated significantly with scores on the FTND,<sup>299</sup> as well as with specific genetic polymorphisms in the dopamine reward pathway.<sup>360</sup> These factors should be considered in laboratory assessment of cue-induced craving as an endophenotype.

## ***Description of Craving Measures and Procedures***

### **Measures of Craving**

Craving is typically viewed as the desire or urge to smoke,<sup>361</sup> although others have argued that craving should be reserved for extreme urges to use a drug.<sup>362</sup> Craving is often synonymous with the self-reported desire to smoke, but craving as a clinical phenomenon is believed to have affective, cognitive, and behavioral dimensions,<sup>363</sup> which can be assessed “objectively,” thus offering the potential for being endophenotypes of dependence. Although abstinence-induced craving has been assessed primarily with self-report, measures aiming to capture these other dimensions have been used in studies of abstinence-induced and cue-induced craving and will be discussed below.

***Self-Report Measures.*** Craving, whether due to abstinence or cue exposure, is typically assessed via a number of self-report measures, ranging from single items asking how strong is the desire or urge to smoke (e.g., on Likert or 0–100 visual-analog scales ranging from none to extremely)<sup>139</sup> to multi-item validated scales, the most popular of which is the Questionnaire on Smoking Urges (QSU).<sup>361</sup> Notably, the QSU has two factors: the first taps anticipation of pleasurable effects (thought to reflect positive reinforcement from smoking), and the second taps anticipation of relief from aversive mood effects of abstinence (reflecting negative reinforcement). The factors have high reliability (>.90). The QSU has briefer 10-item<sup>364</sup> and 4-item<sup>363</sup> versions, although the 4-item version generates a single score. The authors of this chapter assessed the test-retest reliability of this 4-item version of the QSU in 54 smokers who abstained overnight on each of two days; the correlation between days was 0.76, ( $p < .001$ ), showing strong reliability (unpublished data). Moreover, the decrease in this measure of craving following



ad lib smoking was also significantly correlated between days,  $r = .48, p < .001$ . Other measures of craving include the craving subscale of the Shiffman-Jarvik Withdrawal Scale<sup>365</sup> and the Tobacco Craving Questionnaire.<sup>366</sup> Self-reported craving in response to auditory vignettes about smoking (i.e., imagery) appears to be stable and reliable.<sup>367</sup> To determine abstinence-induced craving, craving is typically measured during ad lib smoking, prior to quitting, and then intermittently over hours or days after abstaining. Similarly, cue-induced craving is usually assessed during a neutral baseline condition and then intermittently over seconds, or at most minutes, following presentation of cues.

Measures of craving other than self-report have been commonly used to assess cue-induced craving, although they should be equally applicable to assessing abstinence-induced craving. Such “objective” measures of craving may have promise as endophenotypes and include psychophysiological, cognitive, and behavioral responses, described below.

***Psychophysiological Measures of Craving.*** Since both tobacco abstinence and drug-related cues involve attentional, affective, and motivational processes, psychophysiological measures reflecting these processes may be potential endophenotypes for craving. These measures include heart rate (HR), electrodermal activity (sweat gland activity in the skin), and skin temperature. HR has been examined as both phasic decreases (rapid changes over a few seconds), which tend to reflect acute attentional processes, and tonic increases (changes over a few minutes), which tend to reflect motivational or affective processes. In a meta-analysis of cue reactivity craving studies, Carter and Tiffany<sup>363</sup> calculated the following effect sizes for these responses to smoking cues: 0.21 for tonic HR, 0.44 for electrodermal activity, and  $-0.07$  for skin temperature,

with the first two being clearly significant. By contrast, these authors reported a very large effect size of 1.18 for self-reported craving in response to cues. (Comparable effect-size values were found for responses to cues for other drugs, except HR response to opiate cues, which was not significant.) Thus, the sensitivity of psychophysiological measures to cues remains a question for research on individual differences in these responses to cues.

### ***Cognitive Measures (attentional bias).***

A subsequent approach examined the magnitude of attentional bias toward smoking-related stimuli (e.g., words) in a variation on the Stroop interference task. In this procedure, which has been used with other drugs of abuse,<sup>368</sup> subjects are shown words related to smoking (e.g., tobacco, smoking, ashtray, puff, urge) or not related (i.e., control condition), with each word presented in a different color. The task is to respond quickly with the color of the word (i.e., information-processing reaction time). Reaction time slows when smoking-related words are presented, indicating increased allocation of attention to those words.

### ***Procedures to Elicit Cue-Induced Craving***

The procedures used to elicit craving in response to cues are almost as diverse as the dependent measures of craving. The most common approaches include presentation of

1. In vivo smoking cues, such as a lit cigarette (and including having the subject lighting and holding it) or the sight of the subject's preferred brand.<sup>351</sup>
2. Photos of smoking-related stimuli, such as people smoking or a lit cigarette in an ashtray.<sup>352</sup>
3. Imagery-evoking thoughts of smoking, such as by auditory presentation of vignettes describing a common situation in which a strong desire to smoke occurs (e.g., work stress).<sup>179</sup>



Even newer approaches include use of virtual reality techniques to present visual smoking cues.<sup>369</sup> A variation on these approaches is to personalize them, such as by using photos of pictorial stimuli from the smoker's actual environment that are associated with his or her smoking, rather than the typical use of generic smoking-related photos. Research has demonstrated that pictorial stimuli of environments where smoking often occurs, but without any explicit smoking-related stimuli (e.g., a bar, but with no ashtrays or cigarettes), can increase self-reported craving.<sup>352</sup>

Each of these approaches elicits reliable increases in self-reported craving, although in vivo cues may be most robust. Yet, simply the presence of cues is insufficient to elicit craving. For example, cigarette availability is a clear moderator of craving response to cues, as craving increases much less in response to cues when subjects know that smoking is not possible compared to when they are told that smoking is possible.<sup>370</sup> Expecting to be able to smoke also influences the magnitude of fMRI responses in the prefrontal cortex to smoking cues.<sup>358</sup> Thus, the prospect of being able to act on cravings to smoke may be necessary for cues to induce motivational effects.

### ***Genetic Influences on Craving***

There are no published heritability or family-based studies that elucidate the overall contribution of genetic inheritance to abstinence-induced or cue-induced craving. However, three studies examined associations of genes in the dopamine reward pathway with different measures of cue-elicited cravings. Consistent with neuroimaging evidence for increased activation in the dopamine reward pathway, Hutchison and colleagues<sup>371</sup> reported that smokers carrying the \*7-repeat allele for the *DRD4* gene reported increased craving in response to in vivo smoking cues compared

to those homozygous for the shorter-repeat alleles. Similar results were seen in a neuroimaging study by McClernon and colleagues<sup>372</sup> in that those with the \*7-repeat allele showed greater activation of right superior frontal gyrus and right insula in response to pictorial smoking cues versus control cues, relative to those without the \*7-repeat allele. The *DRD2* gene \*A1 allele and dopamine transporter (*SLC6A3*) \*9-repeat allele have also been associated with stronger smoking cue-induced craving in a laboratory paradigm.<sup>373</sup> In a PET study, smokers carrying the *DRD4* \*7-repeat allele and *SLC6A3* \*9-repeat allele showed increased dopamine binding following cigarette smoking; however, smoking-related cues were not explicitly manipulated in this experiment.<sup>360</sup> Finally, the serotonin transporter gene *5-HTT* has also been associated with craving as measured by the Stroop task measure of attentional bias among smokers, but not among nonsmokers.<sup>374</sup> While preliminary, these data suggest that genes in the dopamine reward pathway, and possibly the serotonin affective regulation pathway, may be important in cue-induced craving.

### ***Association of Craving with Dependence***

#### ***Abstinence-Induced Craving***

Abstinence-induced craving assessed in the days after quitting often, though not always, predicts the outcome of that quit attempt.<sup>375,376</sup> Abstinence-induced craving is also attenuated by most forms of NRT,<sup>349,377</sup> bupropion,<sup>378</sup> and varenicline,<sup>379</sup> although it is not clear that this is the primary mechanism for the efficacy of these FDA-approved cessation medications.

#### ***Cue-Induced Craving***

Despite some plausibility, available evidence shows no clear demonstration that greater self-reported craving response to smoking cues relates to dependence, as determined by persistence of smoking in a clinical

trial,<sup>380</sup> although dependent smokers have greater craving responses to cues than do nondependent smokers (i.e., chippers) in cross-sectional studies.<sup>381</sup> Moreover, despite the observation that NRT alleviates abstinence-induced craving, self-reported cue-induced craving has not been clearly shown to be influenced by NRT<sup>382,383</sup> or any other effective cessation medication, including varenicline.<sup>384</sup> One study found attenuated craving during a cue reactivity procedure due to active nicotine versus placebo gum, but only in a subset of subjects who were particularly responsive to the cue. All subjects had abstained from smoking for several days, and the effect of the gum was not observed until more than 15 minutes after exposure to the cue, suggesting that nicotine gum attenuated abstinence-induced craving and not cue-induced craving.<sup>385</sup> Yet, a rapid rise in urge to smoke during abstinence often precedes a lapse episode (i.e., smoking of at least one cigarette), even weeks after quitting.<sup>114</sup> Because this rapid rise cannot be attributable solely to the time course of abstinence, it is conceivable that acute increases in craving in response to other types of environmental challenges (e.g., alcohol or work stress) may predict clinical outcome, even if responses to smoking cues per se do not.

In sum, no prospective study has clearly shown that the magnitude of self-reported craving response to cues prior to quitting predicts outcome of a subsequent quit attempt.<sup>380</sup> The only possible exception, out of five, is a study in which reactivity to holding an unlit cigarette prior to quitting predicted time to first lapse and 1-week abstinence in smokers who subsequently quit while using the nicotine patch.<sup>386</sup> However, reactivity did not predict lapse or relapse in smokers who quit while using placebo patch and did not predict outcome in the sample as a whole. The fact that cue reactivity did not predict outcome in those treated with placebo or in the entire sample supports null results in the other studies

attempting to link self-reported cue-induced craving to dependence.<sup>380</sup> A few studies have related psychophysiological responses to cues and clinical outcome, but these findings are not robust and generally have not been replicated. Regarding heart rate, studies have shown that later relapse risk is related to larger increase in HR response to cues,<sup>351</sup> larger decrease in HR response,<sup>387</sup> or is unrelated to HR response to cues.<sup>380</sup> Several studies examining electrodermal response to cues failed to show any relationship to relapse risk.<sup>380</sup>

However, a study published in 2007 reported that neural activation during viewing of smoking cues versus control cues was attenuated in the amygdala following an extinction-based smoking treatment; yet, reduction of cue-induced activation of the thalamus predicted smoking cessation success.<sup>388</sup> Therefore, cessation may be predicted by greater attenuation of neural activation to smoking cues over the early course of treatment. Similar research on cocaine supports the potential validity of this approach, as will be discussed in the “Conclusions” section. Additional studies of this type are clearly needed to confirm the reliability of these findings.

The predictive validity of a cognitively based cue reactivity measure—that is, attentional bias—may be more promising in that several studies by Waters and colleagues<sup>389</sup> have related the magnitude of this response slowing (or attentional bias) to dependence. Notably, the authors<sup>389</sup> showed that greater attentional bias predicts greater risk of lapsing in the first week after quitting, and that a high-dose (35 mg) NRT patch reduces such bias. Waters and Feyerabend<sup>390</sup> also showed that attentional bias is greater after overnight abstinence versus no abstinence and predicts shorter time to first cigarette in the morning, a measure strongly related to cessation outcome, as noted earlier. However, attentional bias was unrelated cross-sectionally to other

measures of dependence or smoking intensity, including FTND, cigarettes per day, and cotinine levels.<sup>389</sup>

In terms of behavioral responses to cues, as far as known, no research has examined the degree to which greater smoking behavior in response to cues prospectively predicts outcome of a quit attempt. Likewise, no cross-sectional comparison was found of cue-elicited smoking response between groups varying in level of dependence.

## Affective Regulation

In addition to the reinforcing effects of nicotine and the ability of nicotine to alter cognitive processes and craving, the effects of nicotine on emotional states may also contribute to nicotine dependence. It has been proposed that in some cases, drug abuse may reflect attempts at self-medication for mental illness.<sup>14</sup> Evidence for this includes the higher prevalence of smoking among those with major depression or schizophrenia; these are conditions with symptoms known to be ameliorated in part by nicotine. However, because the majority of smokers do not suffer from these disorders, a more relevant area of research for understanding basic processes in nicotine dependence is the link between negative affect after abstinence and subsequent smoking. A hallmark of the tobacco withdrawal that usually occurs in most smokers in the first few weeks after quitting is negative affect—that is aversive mood symptoms such as dysphoria, fatigue, sadness, or anxiety.<sup>175,391,392</sup> Relapse during the first few weeks of abstinence is often seen as a means to relieve these symptoms by resuming smoking, which very reliably eliminates negative affect due to withdrawal. Some clinical research indicates that negative affect in the days or weeks after quitting not only is predictive of cessation outcome (i.e., one measure of dependence severity) but also essentially accounts for all the clinically predictive

value of total withdrawal severity itself. In other words, when the negative affect symptoms of withdrawal are removed from consideration, the severity of the remaining symptoms of withdrawal generally do not predict cessation outcome.<sup>4</sup> Negative affect after quitting may predict cessation outcome better than do common measures of current smoking intensity, such as cigarettes per day.<sup>393,394</sup>

Discussed below is the general biological plausibility of measures of affective regulation as candidates for endophenotypes of nicotine dependence, including the substantial evidence in animal models for genetic control of affective regulation measures. Subsequently, various objective affect responses are described that have been examined in smoking and nicotine research as well as the limited data on the heritability of measures of affective regulation. A large number of measures have been used to assess affective regulation. For ease of reading, their description will be accompanied by the evidence linking responses on the particular measure to dependence rather than presenting that text in a separate subsection.

## Biological Plausibility

### Preclinical Research

Animal studies provide a means for further understanding the complex relationships between nicotine exposure and affect. Nicotine has both anxiolytic and anxiogenic effects, effects that are dependent on many factors including the test of anxiety used,<sup>395</sup> dietary intake,<sup>396</sup> and the dose of nicotine.<sup>397–399</sup> For example, in the black/white box test of anxiety, BKW mice treated with nicotine spend more time in the brightly illuminated white side of the box, thus reflecting reduced levels of anxiety-related behavior.<sup>400</sup> In CD-1 mice, nicotine increases time spent in the open arms of the elevated plus maze, which is another indicator of decreased anxiety.<sup>401</sup>

Nicotine also increases the acoustic startle reflex, a measure of affective reactivity.<sup>242,402</sup> In addition, nicotine infused directly into the raphe nucleus decreases anxiety, as measured by increased social interaction, in hooded Lister rats.<sup>403</sup> However, opposite (i.e., anxiogenic) effects of nicotine have also been observed in rats and mice.<sup>404–406</sup> In addition, systemic administration of nicotine decreases time spent in the open arms of the elevated plus maze, but direct infusion of nicotine into the dorsal hippocampus increased time spent in the open arms in hooded Lister rats, suggesting that the hippocampus may not mediate the anxiogenic properties of nicotine but may be involved in the anxiolytic properties of nicotine in hooded Lister rats.<sup>407</sup> Finally, in both mice and rats, nicotinic agonists have been shown to have properties similar to antidepressants.<sup>408–411</sup>

Genetic variability also contributes to the effects of nicotine on affect in rodent models. For example, nicotine can increase, decrease, or produce no effect on startle depending on the strain of mouse used.<sup>412,413</sup> In a strain survey of open-field activity in BALB, C57, C3H, and DBA mice, nicotine decreased open-field activity in the BALB, C57, and DBA strains but increased activity in the C3H strain.<sup>412</sup>

Genetically modified mice have been extremely useful for understanding both the genetic factors that influence the effects of nicotine on anxiety and for understanding nAChR subtype involvement in the effects of nicotine on anxiety. For example,  $\alpha 4$  knockout mice spend significantly less time in the open arms of the elevated plus maze (reflecting increased anxiety) compared to wild-type controls.<sup>414</sup> Interestingly, mice with a leucine to serine point mutation that results in hypersensitive  $\alpha 4$  nAChRs also show decreased time in the open arms of the elevated plus maze.<sup>415</sup> The results of these two studies suggest that  $\alpha 4$ -containing nAChRs may

mediate anxiety such that overactivation or underactivation of these receptors may increase anxiety. Furthermore, in mice with a single point mutation that results in increased sensitivity of  $\alpha 4$ -containing nAChRs, the dose-response curve for nicotine disruption of the startle reflex was shifted to the left.<sup>416</sup> In  $\beta 2$  knockout mice, nicotine had no effect on startle, but nicotine did disrupt startle in wild-type littermates. These results suggest that genetic factors contribute to the effects of nicotine on startle and that the  $\alpha 4\beta 2$  nAChR may mediate these effects. In  $\alpha 5$  nAChR subunit knockout mice, no change in open-field activity is seen, compared to wild-type mice.<sup>417</sup>  $\beta 3$  knockout mice show more activity in the illuminated open-field arena compared to wild-type mice.<sup>247</sup> Because high illumination is anxiogenic in mice, this increase in activity could be due to changes in locomotor activity, changes in anxiety, or an interaction between the effects of nicotine on anxiety and locomotor activity in the  $\beta 3$  knockout mice. These genetic studies illustrate the complexity of both the genetic underpinnings and the phenotype assessments.

### Human Clinical Research

Clinical research demonstrates that self-reported negative affect is associated with persistence of smoking, supporting the notion that objective measures of negative affect and its change due to abstinence and smoking in chronic smokers may be relevant endophenotypes of dependence. As noted, smoking is much more common among those with a history of major depression. Much other research shows an association between negative affect and smoking. For example, in a study of 202 smokers, nearly one-half of the sample scored in the depressed range and were more likely to report smoking motivated by a desire to reduce negative affect.<sup>418</sup> Similarly, greater depressed mood and anger after quitting smoking predicts risk of relapse.<sup>376,419</sup> However, the momentary level of negative

affect after quitting may be less important than the pattern or trajectory of negative affect over time.<sup>391</sup> A rapid rise in negative affect in a period of hours predicts greater risk of lapsing, but a gradual increase in negative affect in a period of days does not.<sup>420</sup> Moreover, although any lapse increases risk of relapse, as noted in the prior section of this chapter, lapses triggered by negative affect due to “stressful” events are more strongly predictive of relapse than are lapses triggered by activities such as eating or drinking alcohol.<sup>114</sup> Thus, the predictive value of lapses is not uniform but depends on their context, and the presence of negative affect in the lapse context can be more interruptive of efforts to maintain abstinence.

Less evidence links smoking to anxiety, one component of negative affect. In a study that examined the relationship between anxiety sensitivity and drug use, smoking was positively correlated with scores on an index of anxiety sensitivity.<sup>421</sup> In the National Comorbidity Study, current smoking rates were significantly higher among individuals reporting anxiety-related disorders in the past month, including social phobia, agoraphobia, panic disorder, or generalized anxiety disorder, compared to respondents with no mental illness.<sup>422</sup> Of greater relevance to the focus of this chapter, rates of self-reported quitting success (i.e., being a former smoker) was also significantly lower in most of these groups, relative to the general population.<sup>422</sup>

A few studies have examined the affective responses to nicotine or smoking in abstinent smokers, hypothesizing that greater acute self-reported mood response to drug intake would characterize withdrawal relief and could relate to dependence. In two studies, greater reinforcement (i.e., self-administration) from nicotine spray, either in ad lib or choice procedures (see subsection above on “Reinforcement”), was predicted by greater pleasurable mood

effects (reflecting stimulation) from nicotine among briefly abstinent smokers not currently trying to quit permanently.<sup>122,127</sup> Somewhat similarly, Rose and colleagues<sup>423</sup> found that self-report of smoking for stimulation reasons predicted relapse in young adult smokers, as did greater cigarettes per day. Although this self-report of smoking “motives” does not prospectively assess acute mood responses to smoking, it does presumably reflect the general mood response of smokers to smoking, although biases with such self-report measures are considerable.<sup>424</sup> Nonetheless, these data provide a plausible rationale for investigating objective measures of anxiety as potential endophenotypes for nicotine dependence.

### ***Genetic Influences on Measures of Affect in Humans***

Although twin studies have documented the role of genetic factors and gene-environment interactions in mood disorders (e.g., anxiety disorder, major depression),<sup>425–427</sup> as well as in anxiety-related personality traits,<sup>428,429</sup> the heritability of nicotine or smoking effects on anxiety symptoms is not known. However, a study of a large cohort of twins documented heritability estimates of about 25%–50% for self-reported nicotine withdrawal symptoms that are affective in nature.<sup>430</sup> In addition, candidate genes in the dopamine pathway,<sup>431,432</sup> serotonin pathway,<sup>433,434</sup> and opioid pathway<sup>40</sup> have been associated with withdrawal-related affect or moderation of the effects of self-reported affect on smoking behavior. This evidence from self-report measures suggests that laboratory-based measures of affect in chronic smokers may provide useful endophenotypes in future research.

One such laboratory measure, the acoustic startle response, has been shown to exhibit high test-retest reliability in schizophrenic patients and controls, suggesting a trait



component.<sup>257</sup> In a study of 170 female twins aged 18–28 years, the heritability of acoustic startle was estimated to be roughly 70%.<sup>258</sup> There is also evidence for shared genetic variance with the PPI measure of sensory gating described above.<sup>258</sup> No papers were found examining specific genetic variants in relation to the startle response in humans or genetic studies of nicotine effects on the startle response or other objective measures of affect.

Genetic analyses incorporated into functional neuroimaging investigations of affective responses have generated interesting results, however. For example, two studies using fMRI to assess neural responses during presentation of emotional images found increased activation in the amygdala of subjects who carry the short allele of the functional serotonin transporter promoter polymorphism (*5-HTTLPR*) compared with those with the long allele.<sup>435,436</sup> These effects were equally significant in males and females;<sup>435</sup> however, effects of smoking status were not examined. Neural activation in response to unpleasant visual stimuli has also been related to the presence of the low-activity *\*MET* allele for *COMT* (in contrast to the protective effects of the *\*MET* allele for neurocognitive performance).<sup>437</sup> Similarly, individuals who are homozygous for the *COMT \*MET* allele exhibit increased activation in the ventrolateral prefrontal cortex during presentation of faces expressing negative emotions.<sup>438</sup> Thus, genes in both the dopamine and serotonin pathways may contribute to neural activity and emotional reactivity, but the role of nicotine in these effects is unknown.

### ***Description of Measures of Affectivity and Association with Dependence***

#### **Self-Reported Affect**

As with craving, affect (or mood) is usually assessed with self-report measures. Several valid multi-item scales are available,

such as the Positive and Negative Affect Schedule,<sup>439</sup> the Mood Scale of Diener and Emmons,<sup>440</sup> or the Profile of Mood States.<sup>441</sup> These measures were not designed for studies of smoking or even acute drug use but have been shown to be somewhat sensitive to brief drug exposure. Some studies use more specific single items to assess particular moods (e.g., visual-analog scales, from 0 to 100, corresponding to “not at all” to “extremely,” for “stimulated” or “head rush/buzzed”<sup>174</sup>). For example, the most widely used self-report withdrawal scale, the Minnesota Nicotine Withdrawal Scale,<sup>442</sup> is a series of individual symptom items that can be scored individually or combined into a single withdrawal score. Abstinence-induced increases in negative affect are very reliable and peak within a few days after quitting, although some quitters can experience prolonged and/or episodic increases in negative affect.<sup>391,392</sup> In terms of smoking’s acute effects on mood, smoking, and nicotine in particular, dose-dependently increase responses on measures of arousal, vigor, and head rush, which are typically viewed as pleasurable, but also increase tension and jitteriness, which are usually considered aversive.<sup>443,444</sup> However, as noted in the introduction to this section, these effects are seen primarily in abstinent smokers and are minimal in nonabstinent (i.e., nondeprived) smokers,<sup>443</sup> suggesting that these effects may in fact reflect withdrawal relief rather than the direct pharmacological effects of nicotine. Moreover, few pleasurable effects of nicotine are seen in nonsmokers, although they do report aversive effects of nicotine, such as increases in fatigue, along with those adverse effects seen in smokers. In fact, while “head rush” response is associated with greater nicotine reinforcement (i.e., self-administration) in smokers, that same response is inversely associated with nicotine reinforcement in nonsmokers.<sup>128</sup> Thus, the same mood response may be pleasurable in smokers but aversive in nonsmokers.



Persistent smoking is strongly related to the degree to which negative affect (as assessed by several of these measures) increases after quitting, and sometimes in anticipation of quitting (i.e., in the days leading up to the quit day), as each increases the likelihood of relapse and speeds its occurrence.<sup>4,391,445</sup> Thus, abstinence-induced increases in self-reported negative affect are very clearly related to dependence level in chronic smokers. As far as known, no research shows that the magnitude of acute changes in these measures in response to smoking or nicotine predicts persistence of smoking, and some research shows no association. In one prospective study, sensitivity to nicotine's effects on about 12 mood measures or items before a quit attempt were examined for ability to predict withdrawal severity and time to relapse after quitting, and none was significant.<sup>145</sup> A measure of nicotine choice, however, predicted both, showing that the failure of mood responses to predict clinical outcome was not due to inadequate power. In any case, while the degree of self-reported negative affect in the days after quitting strongly predicts smoking persistence, no available research has shown any association between acute mood responses to nicotine or smoking before quitting and subsequent outcome of a quit attempt.

Also, as with craving, negative affect has physiological, cognitive, and behavioral dimensions that cannot be captured by self-report measures, and measures in each of these domains may be potential candidates for endophenotypes of negative affect during tobacco withdrawal. This section integrates a description of the measure with the available data on the relationship to nicotine dependence.

### **Physiological Responses to Abstinence**

Responses to abstinence include physiological changes including decreases in heart rate and in cortisol, a "stress" neurohormone that rises in a period of

minutes following an affective challenge. The magnitude of decline in heart rate is not clearly associated with cessation outcome, but a few studies have related the decline in cortisol to outcome. Al'Absi and colleagues<sup>419,446</sup> found that the larger the drop in cortisol in the first day or two after quitting, the faster will be the time to relapse. Similarly, Ussher and colleagues<sup>447</sup> found that decline in cortisol on the first day of quitting was marginally related to relapse at six weeks in smokers treated with a 15-mg nicotine patch. However, they also showed that the smaller the absolute level of cortisol on the day after quitting, the higher is the self-reported craving and withdrawal, suggesting a link between low cortisol and the aversive symptoms of abstinence. This association was significant even after controlling for number of cigarettes per day before quitting. Moreover, a drop in the *ratio* of another steroid hormone, dehydroepiandrosterone (DHEA), to cortisol during the first week of quitting predicted relapse by the end of the second week.<sup>448</sup> A decrease in this DHEA to cortisol ratio also predicted the increase in withdrawal and the symptom of depression among women, but not in men. Both DHEA and cortisol are released in response to activation of the hypothalamic-pituitary-adrenal axis, which is often associated with stress or negative affect. Thus, greater decline in cortisol or in the DHEA to cortisol ratio in the first days after quitting appears to be a reliable predictor of quitting success and warrants further study. Few other neurohormones have been examined as indices of dependence, but cross-sectional comparisons have been made between hormone levels and current dependence. For example, allopregnanolone and pregnenolone levels were directly correlated with cotinine levels, an index of amount of recent smoking.<sup>449</sup>

### **Startle Response**

A psychophysiological response that is related to affectivity is the startle response.

This response is the magnitude of eyeblink response to a sharp stimulus, usually a brief loud noise, but also can be an electrical pulse; it is thought to reflect a defensive response to threat that may be mediated by the brain's limbic system (i.e., amygdala).<sup>450</sup> Recall that the PPI of the startle response was discussed previously as a measure of sensory processing. However, the startle reflex itself is related to affect. Research in emotion has shown clearly that negative mood induction increases, and positive mood induction decreases, the magnitude of the startle response.<sup>451</sup> Thus, greater affectivity should be evidenced by larger startle responses. However, a few studies have found no difference in startle magnitude between nondeprived smokers, briefly deprived smokers, and nonsmokers, either during baseline (i.e., in the absence of mood induction)<sup>452</sup> or in response to negative mood induction.<sup>453</sup> Moreover, in within-subjects comparisons, neither overnight abstinence<sup>454</sup> nor acute smoking, has consistent effects on acoustic startle response.<sup>455</sup> Notably, however, one study found that smokers who were able to quit for 24 hours had larger startle response before quitting, and quitting decreased startle response 24 hours later.<sup>456</sup> Startle magnitude was not significantly correlated with scores on the Fagerström Tolerance Questionnaire. This result is contrary to the notion that greater affectivity as indexed by startle response is associated with greater dependence, in that greater startle response before quitting should predict lower, not greater, ability to quit. Similarly, the decline in startle response 24 hours after quitting is the opposite of what would be expected in light of the commonly observed increase in negative affect after quitting.

### **Distress Tolerance**

Individual differences in ability to tolerate distress or to persist with frustrating tasks may put smokers at greater risk for relapse during a quit attempt. For example, Brandon and colleagues<sup>457</sup> have shown

that lack of persistence with a challenging psychomotor task—that is, mirror tracing (tracing a pattern when seeing its reverse image in a mirror)—before quitting prospectively predicts greater risk of relapse 12 months after quitting. In a similar line of research by Brown and colleagues, responses on a self-report measure of distress tolerance were found to predict early smoking relapse.<sup>458</sup> The authors made the point that *how* one reacts to distress, rather than severity of withdrawal per se, may be key to relating withdrawal to risk of relapse. Thus, rather than absolute severity of negative affect during withdrawal being the only important factor, it may be the smoker's cognitive appraisal of that negative affect that interacts to predict relapse.

### **Psychophysiological Response to Acute Stressors**

Another approach to studying affective regulation during tobacco abstinence is to test psychophysiological responses to acute stressors (i.e., negative affect in response to contrived challenges rather than to smoking abstinence). Acute stress increases smoking behavior in smokers and increases relapse after a quit attempt.<sup>459</sup> One notion is that abstinence removes an important method of coping with acute stress—that is, cigarette smoking—which may aid ability to cope via behavioral (e.g., perceived control) or pharmacological (direct actions of nicotine) mechanisms.<sup>4,459</sup> Acute stress can mimic some of the symptoms of withdrawal, particularly negative affect. Thus, loss of ability to cope with stress may also reflect loss of ability to cope with the symptoms of withdrawal and could relate to the distress-tolerance characteristic noted above.

Psychophysiological responses to stressors may also relate to level of distress, given that systolic blood pressure response to the stressful tasks of mental arithmetic and speech preparation (having to quickly prepare a public speech) predicted faster relapse in women smokers. Male smokers

did not show this association, although greater postural hypotension (drop in systolic blood pressure after standing) predicted faster relapse in men.<sup>460</sup> Complicating this picture further, another study found that attenuated, not larger, adrenocorticotrophic hormones, cortisol, and diastolic blood pressure responses to mental arithmetic and speech preparation predict faster relapse at four weeks.<sup>419</sup> Thus, psychophysiological responses to stressors are not consistently related to cessation outcome. Yet, as would be expected from the prior discussion of self-report measures of affect, those who relapsed had greater self-reported negative mood and withdrawal at baseline, as well as greater self-reported craving response to the stressor. Notably, these predictors of relapse remained significant after controlling for smoking history characteristics.

In summary, an increase in self-reported negative affect, and perhaps drops in cortisol and DHEA to cortisol ratio responses to abstinence, have been shown to predict faster relapse to smoking after quitting (i.e., smoking persistence). Few other measures of affective regulation have been shown to have consistent associations with cessation.

## Impulse Control

Behavioral impulsivity is an important potential area of endophenotype measures for at least two reasons: (1) personality characteristics associated with impulsivity increase risk of becoming dependent on a number of drugs, including tobacco (as discussed in detail in chapter 8), and (2) difficulty concentrating, which can be related to impulsivity, is a reliable symptom of tobacco withdrawal that is clearly relieved by both smoking and nicotine alone (i.e., NRT). In the smoking literature, substantial research has been conducted in both of these areas, but relatively little of it has focused on relating outcome of a

cessation attempt to individual differences in the personality characteristic of impulsivity or in withdrawal symptoms related to impulsivity.

## Biological Plausibility

### Preclinical Research

Much less research has examined effects of chronic nicotine and nicotine withdrawal on impulse control in rodent models. In one study by Dallery and Locey,<sup>461</sup> rats were trained on a delayed reinforcement paradigm in which they could choose either an immediate reward of a single food pellet or a larger reinforcement of three pellets that had a variable delay. The choice of the smaller, immediate reward over the larger, delayed reward is considered an impulsive choice (parallel to the delay discounting measure discussed below). Chronic nicotine, but not acute nicotine, increased impulsive choice in this study, with persisting effects for 30 days after termination of chronic nicotine treatment. These findings suggest that chronic nicotine alters neural function, resulting in a long-lasting increase in impulsivity.

Although less is known about strain differences in nicotine effects on impulsive behavior in rodents, a few studies suggest that nicotine's effects on impulsivity may be mediated by nAChRs. For example, spontaneously hypertensive rats, a rat strain often used as a model for ADHD, have decreased nAChRs in cortical and subcortical brain regions compared to Wistar-Kyoto rats; however, chronic nicotine produces nAChR upregulation only in the Wistar-Kyoto rats.<sup>462</sup> Agonist compounds selective for  $\alpha 4 \beta 2$  nAChRs reduce spontaneous alteration behaviors in a Y-maze task in SHR,<sup>463</sup> and DH $\beta$ E, a competitive  $\alpha 4 \beta 2$  antagonist, blocks nicotine's effects on impulsive responding.<sup>464</sup> Much less is known about genetic modulation of nicotine effect on impulsivity than on other endophenotypes examined

in this chapter. However, the Dallery and Locey<sup>461</sup> study described above suggests that effects of chronic nicotine in smokers could maintain dependence and facilitate relapse during abstinence attempts as smokers may favor the immediate gratification of the cigarette over the delayed goals associated with remaining abstinent.

### **Human Clinical Research**

The role of impulsivity in the onset of smoking is discussed at length in chapter 8. Here, the focus is on a smaller set of studies on the role of impulsivity in chronic smokers. As described in the “Attention and Vigilance” subsection above, adult smokers with current or childhood ADHD have more severe nicotine withdrawal after quitting, compared to smokers without any ADHD history.<sup>270</sup> In the general population of smokers, the greater the increase in hyperactive/impulsivity symptoms after quitting, the greater the probability of relapse.<sup>273</sup> Moreover, among smokers with a history of major depression, those with higher scores on the Barratt Impulsivity Scale, a common self-report measure, relapse more quickly.<sup>465</sup> Among smokers not trying to quit, those higher in impulsivity on the Barratt Impulsivity Scale report greater relief of negative affect from a nicotine versus denicotinized cigarette during a laboratory mood-induction procedure.<sup>466</sup> Such smokers also anticipate greater expectations for positive and negative reinforcing effects of smoking.<sup>467</sup> This finding is in contrast to findings from an earlier study of treatment-seeking smokers in which self-reported hyperactivity symptoms did not correlate with smoking motives.<sup>271</sup>

### ***Description of Impulsivity Measures***

In addition to the common self-report measures of impulsive personality characteristics, several “objective” measures of impulsivity and behavioral inhibition may serve as potential endophenotypes of dependence.

### **Delay Discounting**

Delay discounting measures the tendency to choose smaller, immediate rewards over larger, delayed rewards and is believed to reflect impatience and a desire for immediate gratification. Drug dependence is often viewed as choosing an immediate reward, drug use, over larger, delayed rewards—namely, the long-term gains in health outlook by abstaining from drug use. (Long-term gains in choosing abstinence among illicit drug users include increased employability, improved family relations, reduced legal problems). Delay discounting has been used in a variety of studies of drug dependence in both humans and nonhuman animals.<sup>468</sup> In this task, participants are given repeated choice options between a large monetary option, to be made available to the participant after different durations of delay, such as in one day, one week, one month, six months, and a year, versus different amounts of lesser, immediate rewards.<sup>469</sup> The smallest amount of immediate reward the participants select in preference to the larger, delayed reward at each duration of delay reflects the degree to which they discount the value of the delayed reward. Plotting these choices leads to a temporal discounting function for each individual, which can be averaged for subgroups. The sharper the decrease in the function (i.e., the smaller the current reward chosen over the delayed reward), the greater the discounting and, presumably, the more impulsive the subject. Performing this task involves sorting (choosing) actual cards containing the different money and delay choices,<sup>469</sup> but the task is easily presented by computer presentation of the choices and having subjects choose via computer key. This task is also commonly done with hypothetical choices, rather than actual choices. Some research suggests that findings are similar regardless of whether actual or hypothetical choices are offered,<sup>470</sup> but other studies suggest that actual choices may be more sensitive.<sup>471</sup> A variation on this task involves probability discounting,

or greater discounting of smaller, more certain rewards in favor of larger, less certain rewards.<sup>472</sup>

### Go/No-Go Task

The go/no-go task requires a subject to make a motor response according to a conditional rule (e.g., in response to a target stimulus) and to inhibit a motor response according to a similar rule.<sup>473–475</sup> For example, a downward-pointing triangle may be used as a target stimulus and an upward-pointing triangle as the nontarget stimulus. Although this task is conceptually similar to the CPT described above, the rate and reaction time for commission errors (i.e., responses made to the nontarget or no-go stimulus) provides a measure of behavioral inhibition.

### Stroop Task

The Stroop task measures the ability to inhibit a prepotent response to a stimulus and, therefore, provides an objective measure of response inhibition of relevance to impulsivity traits. In this task, subjects view a series of words printed in color (e.g., either green or red) and are instructed to identify the color of the ink used. In some cases, the word color and the ink color match (e.g., the word *red* written in red ink; congruent word), and in other cases, the word and color are incongruent (e.g., the word *green* written in red ink). The classic Stroop effect is the difference in reaction time for naming colors for incongruent versus congruent words. This task has been adapted as a measure of attentional bias, as noted previously.<sup>368</sup>

### Genetic Influences on Impulsivity Task Responses in Humans

A few studies have examined the heritability of laboratory-based measures of impulsivity. Using the standard Stroop task as a measure of resistance to interference in 290 twins, Stins and colleagues<sup>476</sup> reported a heritability of 50% for the Stroop effect (i.e., reaction-time difference). For the

go/no-go task, among 400 twin pairs, heritability for mean reaction time (across fast and slow tasks) was 60%, and the heritability of commission error rates was 18% for the slow condition and 38% for the fast condition.<sup>477</sup> Groot and colleagues<sup>478</sup> studied 237 healthy twin pairs and found differences in heritability estimates by gender. For example, the commission rate heritability on the go/no-go task was 36% among females and 53% among males. In a combined assessment of performance on the go/no-go task and ERPs, Anokhin and colleagues<sup>479</sup> showed that about 60% of the variance in electrophysiological responses during the task was attributable to genetic influences. The go/no-go task also exhibits high heritability in extended pedigrees with schizophrenia.<sup>480</sup>

Associations of specific candidate gene variants with laboratory measures of impulsivity have been examined in a few studies. Cornish and colleagues<sup>481</sup> studied 58 boys scoring above the 90th percentile on ADHD diagnostic symptoms and 58 scoring below this cutoff. Children homozygous for the *\*10*-repeat allele of the dopamine transporter gene had poorer performance on a response inhibition task, independent of ADHD symptoms. Three studies have examined genetic associations with performance on the go/no-go task. Among 133 children with ADHD, those carrying the *\*7*-repeat allele of the *DRD4* gene had greater impulsivity, faster reaction time, and reduced accuracy, compared to those with the shorter-repeat variants.<sup>482</sup> There is also evidence that delay discounting is associated with an interaction between the *DRD2 TAQ1 \*A1* allele and the *DRD4 VNTR* (*\*7*-repeat) allele.<sup>483</sup>

Two genes involved in the metabolism of dopamine have been associated with laboratory measures of impulsivity. In one study, a monoamine oxidase A gene polymorphism was linked with performance on the go/no-go task.<sup>484</sup> In two other studies,



the *COMT VAL/MET* genotype described above was associated with performance on the Stroop task,<sup>235,485</sup> with an interaction between the *DRD2 TAQIA* variant and *COMT* variants in the earlier study.<sup>485</sup>

Emerging evidence also supports an association of genetic polymorphisms in the serotonin pathway with endophenotype measures of impulsivity. For example, a study in 2006 showed a relationship between the number of commission errors on the go/no-go task and the *\*A-1438A* allele of the serotonin receptor 2A gene *5-HT2A*.<sup>486</sup> Of particular relevance to endophenotypes for nicotine dependence, one study suggests that a performance on a modified “smoking stimuli” Stroop task in smokers is associated with the promoter polymorphism in the serotonin transporter gene;<sup>374</sup> however, this modified Stroop task may be measuring attentional bias to smoking cues rather than response inhibition per se. These data are preliminary but suggest that genetic variation in the dopamine and serotonin pathways may play a role in impulsive behavior as assessed by objective laboratory measures.

### ***Association of Impulsivity Task Responses and Nicotine Dependence***

Current smokers often, but not always, show greater delay discounting than never smokers or even former smokers,<sup>469,472,487,488</sup> and cigarettes per day are correlated with degree of delay discounting,<sup>489</sup> suggesting a linear relationship between amount of smoking intake and impulsivity. However, although greater delay discounting was associated with greater smoking frequency in one laboratory study, nicotine versus placebo patch did not influence delay discounting.<sup>490</sup> The specific procedures used may moderate the findings in laboratory studies of delay discounting. For example, in one study, brief abstinence increased delay discounting of both cigarettes and money when they were actually available,

but no delay discounting was seen when the choices were hypothetical.<sup>471</sup> Also, because lower education is associated with greater delay discounting,<sup>491</sup> education needs to be controlled in comparisons between groups. Despite common findings of greater delay discounting in smokers versus nonsmokers, there appears to be no reliable difference in probability discounting.<sup>472,489</sup>

Less is known about the relationship of objective laboratory measures of impulsivity with nicotine dependence or smoking cessation outcome. In one study of adolescent smokers, those with higher scores on the delay discounting measure were more likely to relapse.<sup>300</sup> However, in a study of schizophrenics seeking treatment for smoking, the Stroop task did not predict smoking cessation success.<sup>301</sup>

## **Discussion and Recommendations for Future Research**

This final section reviews findings on the potential for the measures discussed here as endophenotypes for dependence in chronic smokers and outlines future directions for this research. Each putative endophenotype will be addressed within its broad area in the following subsections on “Motivational Effect Endophenotypes” and “Acute Smoking or Abstinence Effect Endophenotypes.” The findings are summarized in tables 9.1 and 9.2, respectively.

### **Motivational Effect Endophenotypes**

Measures of the motivational effects of nicotine would be expected to offer greater promise as endophenotypes early in this research effort, as they are more proximal to dependence, as indicated in figure 9.1. As noted, the frequency and persistence of drug reinforcement is a central feature

**Table 9.1 Putative Endophenotypes for Nicotine Dependence: Motivational Mechanisms and Nicotine or Abstinence Effects**

Measure	Biological plausibility	Standard, objective, and reliable	Evidence of genetic influence	Linked to dependence
Reinforcement				
Ad lib self-administered	++	+	±	+
Nicotine choice	+	+	+	+
Behavioral economics	+	+	0	0
Progressive ratio	+	+	0	0
Reward				
Self-report of hedonic effects	+	+	0	±

Note. ++ = strong confirmatory evidence; + = some confirmatory evidence; ± = little or equivocal evidence; 0 = no available evidence.

**Table 9.2 Putative Endophenotypes for Nicotine Dependence: Acute Smoking or Abstinence Effects**

Measure	Biological plausibility	Standard, objective, and reliable	Evidence of genetic influence	Linked to dependence
Physiological				
Resting EEG	±	+	+ <sup>a</sup>	0
ERP	±	+	+ <sup>a</sup>	0
PPI	+	+	+ <sup>a</sup>	0
Cognitive function				
Attention	±	+	+ <sup>a</sup>	0
Working memory	±	+	+ <sup>a</sup>	0
Craving				
Abstinence-induced				
Self-reported urge	++	++	0	+
Cue-induced				
Self-reported urge	++	++	±	±
Psychophysiological	±	+	0	—
Cognitive/attentional bias	±	+	±	+
Affective regulation <sup>b</sup>				
Abstinence-induced				
Self-reported negative affect	++	+	0	++
Physiological	±	+	+ <sup>a</sup>	+
Startle	±	+	+ <sup>a</sup>	0
Distress tolerance	+	±	0	+
Stress/physiological	+	+	0	±
Impulse control				
Delay discounting	+	+	0	0
Go/no go	±	+	+ <sup>a</sup>	0

Note. EEG = electroencephalogram; ERP = event-related potentials; PPI = prepulse inhibition; ++ = strong confirmatory evidence; + = some confirmatory evidence; ± = little or equivocal evidence; 0 = no available evidence; — = some contrary evidence.

<sup>a</sup>Evidence regarding the measure in general, no evidence for effect of abstinence or acute smoking.

<sup>b</sup>Virtually no evidence of acute effects of smoking on affective regulation was associated with dependence. Consequently, those measures are not included here; only measures during smoking abstinence are included.

of dependence and, therefore, acute laboratory measures of the frequency and persistence of reinforcement do not require extensive assumptions about the link between these measures and dependence. Measures of ad lib smoking or nicotine self-administration and nicotine choice procedures generally show some of the expected relationships between responses and simple manipulations of smoking abstinence. These measures are also fairly objective and reliable, and there is some evidence for associations with candidate genes; however, the heritability of nicotine self-administration measures is unknown.

The behavioral economic and PR self-administration procedures have received less scrutiny, particularly with regard to genetic influences. However, these are conceptually similar to self-administration measures and are comparably objective and reliable; thus, they may have similar strengths and characteristics, such as being heritable. However, aside from the choice procedure, few of these measures have been related prospectively to dependence by predicting outcomes of a quit attempt, ultimately the key clinical utility of this research.

In terms of future directions for reinforcement measures, use of the PR is common in animal genetic models and for medication screening, and it warrants more attention in human studies. To enhance the sensitivity of this approach, methodological studies to determine the optimal duration of prior abstinence, timing of drug administration, rate of escalation of the PR schedule, and session length would be valuable.

Another procedure that could be adapted to assess individual differences in some aspects of relapse proneness (i.e., dependence as indexed by smoking persistence) is the “programmed lapse” procedure.<sup>492</sup> In this procedure, smokers are required to abstain for a few days and then instructed to either

smoke a few cigarettes to simulate a lapse or to not smoke (control condition). All are instructed to then continue to maintain abstinence, and the measure of interest is duration of abstinence after the simulated “lapse” point. This procedure is sometimes viewed as comparable to the “reinstatement” procedure widely used in animal research as an analog to relapse,<sup>493</sup> although there are substantial limitations of reinstatement as a model for human drug relapse.<sup>494</sup> In any case, some aspects of the programmed lapse procedure could be used to assess each of the phases of smoking relapse in humans: (1) time to first lapse could be examined by instructing subjects to abstain and then prospectively assessing the time to first cigarette,<sup>495</sup> (2) time interval between first and second lapse is essentially what is already determined by the existing programmed lapse procedure,<sup>492</sup> and (3) time to relapse would simply require more extended follow-up to determine when the criteria for relapse (e.g., seven consecutive days of any smoking)<sup>496</sup> are met. For each of these measures, subjects who are able to abstain for longer periods presumably should be those able to quit for longer periods in an actual quit attempt, but this would need to be verified. A more practical measure of persistence of abstinence may be to simply see if the smoker is able to quit for 24 hours, which differentiates high- and low-dependent smokers making an actual quit attempt<sup>115</sup> or not trying to quit permanently.<sup>497</sup> However, this approach results in a dichotomous measure (able versus unable to abstain), which may be insensitive for use in other research relating the measure to other factors.

The other measure within this broad area, smoking or nicotine “reward,” has less evidence supporting its use as an endophenotype, as it is not yet measured in humans in an “objective” way. However, these measures, generally obtained in humans via self-report of “liking” or “satisfaction,” are easy to assess and are

reliable. The magnitude of smoking or nicotine “reward” has strong biological plausibility, and there are objective measures in animals that are thought to reflect reward (e.g., CPP and ICSS). Thus, these measures hold promise as potential endophenotypes for dependence in human smokers, if human equivalent measurement procedures can be found. Although there are obvious impediments to developing brain stimulation measures of reward threshold, it seems plausible that human models of CPP could be developed and validated. However, such complex measures may not add significantly to the armamentarium of human laboratory models; perhaps more attention should be devoted to assessing genetic associations with self-report measures of nicotine reward within the context of other laboratory paradigms.

A key issue that pertains to research on all of the measures discussed in this chapter, not just self-administration and reward measures, is the failure of virtually all laboratory studies of these measures to assess them in smokers preparing to quit. The motivational effects of smoking and nicotine are clearly different in smokers preparing to quit than they are in smokers with no interest in quitting.<sup>141</sup> There is reason to think that the effects of brief abstinence and the acute effects of smoking or nicotine on cognitive, affective, and other functioning may vary depending on whether the subjects are smokers preparing to quit or are not interested in quitting permanently. If so, use of non-treatment-seeking smokers (i.e., those not trying to quit) in this research may contribute to the failure of many of these measures to show sensitivity to dependence. Use of such smokers is not surprising; these procedures were adopted from animal research, which, perhaps necessarily, has focused only on the acquisition and maintenance of drug self-administration. Animal studies have not been used effectively to model “voluntary” abstinence from drug use, as in human

quit smoking attempts,<sup>494</sup> and none of the procedures directly assesses ability to *maintain abstinence*, a critical index of dependence. Thus, differences in quitting motivation between laboratory research participants and smokers in clinical studies may impede the development and validation of brief laboratory-based behavioral procedures that may serve as endophenotypes.<sup>141</sup>

## Acute Smoking or Abstinence Effect Endophenotypes

The cognitive, affective, and behavioral impulsivity measures discussed in this section have at least some biological plausibility and preclinical data to support nicotine effects. Further, many of these constructs can be assessed in a very objective and reliable manner. Some, notably the measures of sensory processing, attention and vigilance, working memory, and impulsivity have clear evidence of heritability. However, this evidence pertains to responses on these measures in general rather than to acute responses on these measures to smoking or abstinence.

Since acute smoking or abstinence effects on these measures are thought to be more distal to nicotine dependence (figure 9.1), these measures require a greater leap from the underlying mechanisms responsible for these effects and processes to nicotine dependence. Consistent with this assumption, virtually none of the measures in this broad area have been directly associated with dependence in chronic smokers, especially as predictors of smoking persistence during a quit attempt, the gold-standard index of dependence in smokers adopted in this chapter. Yet, virtually no evidence links any of these objective measures with persistent smoking in chronic smokers, with the exception of abstinence-induced self-reported craving and negative affect and perhaps hormonal responses to abstinence (cortisol or related measures). It is important to note that lack of research

attention, rather than disconfirmatory findings, characterize the research in this broad area.

Other objective measures with preliminary support for a relationship to dependence are the attentional bias measure of cue-induced craving<sup>389</sup> and the affective regulation measure of “distress tolerance,”<sup>457,458</sup> which are not strictly acute responses to smoking or to abstinence but are more traitlike. These measures deserve further attention with respect to heritability of smoking and abstinence effects as well as associations of candidate genes. Evidence that alcohol priming can alter attentional bias to smoking cues suggests a “state” component as well.<sup>498</sup> Such cross-substance paradigms may provide interesting endophenotypes for genetic studies as well.

Cue-induced craving has substantial biological plausibility on the basis of preclinical and neuroimaging studies. However, thus far, cue-induced craving has virtually no validity as an index of dependence as determined by cessation outcome.<sup>380</sup> Furthermore, NRT has no effect on cue-induced craving, whether in smokers wanting or not wanting to quit permanently.<sup>382,383,386</sup> In contrast, NRT robustly reduces abstinence-induced craving, even acutely in those not trying to quit,<sup>377</sup> and reduces risk of relapse.<sup>349</sup> Yet, olanzapine, an antipsychotic medication not known or proposed to be efficacious for smoking cessation, nevertheless attenuates cue-elicited craving to smoke in healthy smokers.<sup>499</sup> Thus, there appears to be no clear link between the magnitude of cue-induced craving or influences on this type of craving and indices of dependence in adult smokers.

Some of the difficulty with “reactivity” research could be lack of generalizability between the cues used (i.e., the independent variables) and the stimuli that elicits craving and lapses in the smoker’s natural environment. Research has demonstrated that photos of personalized contexts for

smoking (e.g., one’s favorite bar) can elicit as robust an increase in self-reported craving as more typical cues, such as photos of lit cigarettes,<sup>352</sup> and stronger craving than generic photos of the same contexts (e.g., a typical bar). Such research may also benefit by using other types of stimuli that reflect situations tied to smoking lapses but do not directly involve smoking, such as familiar stressors faced by the smoker. For example, in a study of cocaine abuse patients, Sinha and colleagues<sup>500</sup> found that self-reported craving for cocaine in response to a personalized stress-related imagery script, but not to a personalized cocaine-related script, predicted faster relapse to cocaine use. Thus, greater generalizability in reactivity may result from use of personalized cue stimuli or stimuli that otherwise are more representative of the common relapse situations in a smoker’s environment, and reactivity to such cues may be more predictive of relapse after quitting.

Alternatively, the problem with the lack of predictive validity of cue reactivity in the available studies may stem from the responses assessed—that is, the dependent variables—rather than, or in addition to, the independent variables used. The vast majority of studies assess self-reported craving, although some also assess psychophysiological responses.<sup>380</sup> Perhaps broadening the reactivity responses may reveal some that are more strongly tied to relapse, as suggested in the small preliminary study by McClernon and colleagues<sup>388</sup> noted previously. For example, in addition to showing that self-reported craving in response to stress imagery, but not to cocaine imagery, predicted cocaine relapse, the study noted above by Sinha and colleagues<sup>500</sup> also found that greater corticotrophin and cortisol responses to the stress imagery predicted higher amounts of cocaine used per lapse occasion during the follow-up period, although these responses were not related to time to relapse. Somewhat similarly, it was found that fMRI



measurement of brain activation in response to cocaine-related videotapes predicted subsequent relapse in cocaine patients, but self-reported craving in response to the videotapes did not.<sup>501</sup> However, given that attenuated physiological responses, including cortisol, to acute lab-based stressors were shown to predict smoking relapse,<sup>419</sup> it is not clear that heightened responding to stimuli should necessarily be of more interest than blunted response.

Consistent with the notion that cue reactivity research may need to reconsider its dependent measures, such studies may benefit from assessing smoking behavioral responses to such cues.<sup>380</sup> Because prospective research relating any laboratory measure to cessation outcome can be difficult, one intermediate step may be to determine that cues robustly elicit increases in measures of smoking reinforcement, which may be more likely to relate to dependence than do other craving measures. Animal and human evidence shows that cues can have as much, and often more, influence on drug-taking behavior as the drug nicotine itself.<sup>78</sup> Research from the cocaine field indicates that human laboratory self-administration models are better predictors of the clinical efficacy of medications than are results using self-reported craving as the primary dependent measure.<sup>502</sup> Thus, variability in the degree to which smoking behavior, rather than self-reported craving, is altered by cues could provide a more fruitful direction for cue reactivity research aimed at identifying factors responsible for dependence.

Assessing the influence of cues on reinforcement can be assessed with most of the acute procedures presented above in the “Motivational Effect Endophenotypes” section. For example, the presence of a lit cigarette cue increases responding for cigarette puffs under the highest response requirements (i.e., price) in a variation on the behavioral economics procedure.<sup>147</sup> Also,

rather than simply presenting a pictorial or in vivo cue for the smoker’s observation, as in standard cue reactivity research,<sup>363</sup> research should increase the cue salience by providing virtually the entire smoking experience as a cue via denicotinized (placebo) cigarettes. Here, the smoker experiences not only the sight and smell of the cigarette, but also much of the taste and sensory effects of inhaling smoke, but with no nicotine intake. The availability of credible placebo cigarettes has resulted in an increase in their use in a number of areas of smoking research.<sup>137,149</sup> The magnitude of responses to such smoking, which can be viewed as conditioned responses to smoking cues, may be related cross-sectionally to dependence, as suggested.<sup>503</sup>

## Summary

This chapter describes a series of objective laboratory-based measures of motivational mechanisms and acute smoking or abstinence effects as potential endophenotypes for nicotine dependence. Although the motivational measures—in particular, ad libitum self-administration and nicotine choice—have been related to dependence, data on heritability and genetic associations are lacking. The converse is true for measures of acute smoking or nicotine abstinence effects. Sensory, cognitive, affective, and behavioral measures in this area appear to be heritable, and specific genetic associations have been identified; however, this research has not examined genetic influences in the context of nicotine effects, and no data are available to judge the relationship to nicotine dependence. As shown in tables 9.1 and 9.2, there is great potential for research to provide evidence for or against the criteria important for endophenotype measures of nicotine dependence. Although the utility of endophenotypes in genetics research is still a topic of some debate,<sup>52</sup> this debate can only be resolved through rigorous future research.

## Conclusions

1. Nicotine dependence in chronic smokers is characterized by persistent smoking behavior despite knowledge of its harm (e.g., an inability to sustain a quit attempt). Reinforcement measures such as nicotine choice have been related to nicotine dependence, although further research is needed on the relationship between dependence and ad libitum drug self-administration, behavioral choice, and progressive ratio measures. Genetic studies in reinforcement measures in mice indicate a potential for studying the heritability and genetic influence for these behaviors in humans.
2. Limited evidence exists regarding the relation between self-reported measures of reward and nicotine dependence in humans, while animal studies show a potential link between the reward-related measure of conditioned place preference and nicotine dependence.
3. Evidence of heritability and genetic influence has been established for measures of sensory processing, such as resting electroencephalogram activity, event-related potentials, and the prepulse inhibition of startle response, as well as cognitive measures such as attention and working memory. Further research is indicated to investigate the relationship of such measures to nicotine dependence in humans.
4. Self-report measures of abstinence-induced craving have been related to the success of cessation efforts (i.e., dependence), while neither cue-related craving nor psychophysiological measures of craving have been reliably shown to relate to nicotine dependence. The relationship of these measures with genetic factors remains an area for further investigation.
5. Self-reported levels of negative affect following smoking cessation have been strongly related to smoking persistence. Persistence has also been associated with abstinence-induced changes in physiological measures such as cortisol and the dehydroepiandrosterone to cortisol ratio. Other measures of affect have not been shown conclusively to relate to measures of nicotine dependence.
6. Impulsivity and cognitive control measures such as delay discounting, the go/no-go task, and the Stroop interference task have not been shown conclusively to relate to nicotine dependence, while the go/no-go task has shown some evidence of heritability and relation to genetic factors.
7. Overall, the available evidence supports the possibility of endophenotypes for nicotine dependence in chronic smokers on the basis of motivational factors and, to a lesser extent, sensory, cognitive, affective, and behavioral measures. Further research is indicated to help establish a consistent pattern of heritability, genetic influence, and association with nicotine dependence for measures in each of these areas.

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