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Endophenotypes for Nicotine-Dependence Risk at or before Initial Nicotine Exposure

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Characteristics present before or at the time of nicotine exposure may play a key role in identifying individuals at genetic risk for nicotine dependence. This chapter examines the evidence base for several candidate endophenotypes for nicotine-dependence risk at or before smoking and nicotine exposure, including the following:

- *Approach-related smoking risk variables based on psychological traits such as impulsivity, novelty seeking, and extraversion, using laboratory measures for aspects of reinforcement and reward*
- *Avoidance-related smoking risk variables based on psychological factors such as neuroticism, stress, depression, and anxiety, using laboratory measures including personality trait measures, peripheral nervous system (PNS) effects, and neuroendocrine response to cortisol*
- *Control-related smoking risk based on psychological variables such as attention deficit hyperactivity disorder (ADHD), conduct disorders, aggression, and hostility, using laboratory measures including response inhibition, event-related potential (ERP) P300 amplitude, attention, and alertness*
- *Measures of initial response to nicotine exposure, including reinforcement and reward measures of initial sensitivity to nicotine, as well as initial sensitivity to affective and mood responses to nicotine*

Although available evidence shows a link between many of these variables and smoking behavior, further research is needed to establish possible nicotine-dependence endophenotypes from a standpoint of predictive validity, biological plausibility, reliability, and heritability.

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Introduction

This chapter examines potential endophenotypes for risk for (1) initiating and progressing in smoking and (2) responding to the initial nicotine exposure. First, it briefly surveys major within-person risk factors for smoking initiation and progression. It then assesses these from the perspective of potential endophenotypes via a conceptual model of neural circuits that may be relevant to smoking initiation and progression, particularly with regard to a general risk pathway. A general risk pathway indicates a vulnerability that may be shared between nicotine and other drugs; hence, some overlap can be expected in the domains of interest here with those being studied for other drugs such as alcohol. This approach is well justified in view of behavioral genetic evidence of shared genetic liability to the misuse of nicotine, alcohol, and other drugs,¹⁻³ although the degree of shared genetic factors may vary with age.⁴ However, some endophenotypes may be relatively more general and linked to initial attraction to many types of substances (e.g., reward dependence), and others may have greater specificity to trying nicotine (e.g., attentional dysfunction).

The second part of this chapter considers processes occurring in the early stages of nicotine exposure that may increase the likelihood of further exposure to nicotine and subsequent nicotine dependence; it looks at potential endophenotypes at that inflection point, shifting to a pharmacological response model and a more drug-specific pathway. A drug-specific model is justified at this inflection point by evidence that pharmacological response may influence selection of drug use over time. The final section of the chapter discusses the state of the research and offers recommendations for future investigation.

Endophenotypes

An explanatory gap between candidate genes and the presence of symptoms of nicotine dependence necessitates new approaches to identifying genetic liability markers. Smoking risk is an area of study overlapping with numerous complex disorders and traits with which it is correlated. Therefore, a useful strategy may be to identify valid and reliable intervening constructs to link candidate genes and nicotine dependence, as has been suggested for behavioral traits and disorders generally.⁵⁻⁸ The field holds relative consensus that genetic and environmental risk for substance use includes a general risk factor (not specific to one drug) and drug-specific factors.⁹ Intervening constructs need to be identified both at the general level (where they will be shared among several drugs) and at the nicotine-specific level.

These intervening constructs, referred to as *endophenotypes*, can be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, behavioral, or neuropsychological, as long as the endophenotype ultimately enhances the genetic signal for the disorder's causal processes.¹⁰ Most behavioral measures, although providing useful clues, are usually considered less parsimonious than most cognitive or biological endophenotypes given the (presumed) extra steps needed to link them to genes or the proteins for which they code. Further, because genes influencing behavioral and addictive disorders are presumed to operate in the brain, and to be detectable by probes of brain activity (such as cognition), cognitive and physiological measures that can be validated in relation to neural systems are attractive candidates.

Consequently, a neural networks perspective is useful to analyze potential endophenotypes. Such a model can be

adopted to examine behavioral, cognitive, and physiological endophenotypes that may be related to smoking initiation discussed in the first half of this chapter. Nicotine is not a drug of universal exposure. Thus, factors that differentially influence initiation of use, including genetics, are critical. At the same time, once smoking has been initiated, the pharmacological response to the nicotine presumably becomes a key factor in an adolescent's subsequent smoking behavior and progression to nicotine dependence. Therefore, the second part of this chapter moves to a lower (more molecular) level of analysis and considers a pharmacological perspective on smoking progression in conjunction with trait measures.

Assuming an endophenotype can be validated, it can provide a potentially powerful tool for identifying individuals at genetic risk of initial nicotine use and of going on to nicotine dependence (becoming nicotine dependent and staying nicotine dependent), and it can also clarify phenotypic heterogeneity.¹¹ That is, complex traits such as smoking and nicotine dependence are probably due to numerous genes in several pathways, interacting with each other and the environment. Endophenotypes are intended to represent more defined and quantifiable measures that are thought to involve fewer genes and fewer interacting pathways, which ultimately result in the activation of a narrower set of neuronal circuits.¹¹ Because endophenotypes, when valid, are more proximal biologically to the putative genetic influences, they may be more sensitive measures for genetic studies of nicotine dependence.¹² No endophenotypes have been validated for smoking risk; this chapter examines candidate markers that may hold promise as potential endophenotypes.

Several criteria have been advanced to evaluate the validity of a putative

endophenotype.^{7,10,13} The criteria used to evaluate a potential endophenotype for nicotine dependence include (1) predictive validity; that is, it is related to a smoking phenotype of interest (initiation or progression); (2) biological plausibility; that is, it can be linked to specific neural pathways or actions, which can relate directly to candidate genes; (3) reliability; and (4) heritability. Bivariate heritability is not evaluated in this chapter because data are lacking on its relation to smoking initiation and progression. For more discussion of the criteria for an endophenotype, see Waldman and colleagues.^{13,14}

This chapter derives its concept of "endophenotype," which has been criticized as underspecified, from other studies. For example, Szatmari and colleagues¹⁵ suggest that responses that are often considered as potential endophenotypes can be conceptualized as one of three "subtypes," only two of which would be true endophenotypes: (1) component phenotype, (2) intermediate phenotype, and (3) covariate.¹⁵ Component phenotypes capture only one aspect of a multidimensional disorder of interest; they may or may not be a necessary part of the disorder, but they are not a sufficient determinant (i.e., alone they do not fully capture the disorder). Building on the logic of these authors, component phenotypes can be viewed as a portion of the disorder phenotype but not part of the causal chain to it. Intermediate phenotypes, by contrast, refer to a mechanism believed to be part of the causal chain to the disorder; this is the original meaning of "endophenotype" provided by Gottesman.¹⁰ An intermediate phenotype is expected to reflect a predisposition for the disorder in unaffected family members as well as in those already affected. The third subtype, covariates, are really not endophenotypes at all; they are factors related to the disorder of interest but not components of it and certainly not

causal. Part of the goal of research in this area is to determine into which of these subtype categories a candidate measure actually falls (usually it is unknown until investigated). Of most interest in this chapter are markers suspected to be the second type (intermediate phenotypes), although in fact some of these may turn out to be covariates. The reason for emphasizing intermediate phenotypes is that this chapter is focused on those at risk for nicotine dependence but not yet “affected” with the disorder. The next chapter, on putative endophenotypes for dependence after chronic exposure (i.e., in those already “affected”), focuses on component phenotypes.

Rationale for Investigating Nicotine-Dependence Risk Endophenotypes

Like most complex traits, smoking behavior is the result of genetic and environmental influences.¹⁶ Heritability studies of adolescent twins estimate that at least 33% of the variance in smoking initiation (ever smoking), more than 80% of the variance in smoking rate, and 44% of the variance in nicotine dependence may be attributable to genetic factors.^{1,17-19} Genetic factors may be more important in discriminating those adolescents who become nicotine dependent from those who simply initiate and do not progress beyond limited experimentation.^{18,20}

Evidence for smoking heritability has encouraged a growing number of studies examining the role of candidate genes involved in nicotine metabolism and drug reward in adolescent smoking and nicotine dependence. Most of the candidate gene studies have focused on genes directly related to nicotine’s biological action. For example, such studies indicate that genetic variation in enzymes responsible for nicotine metabolism (i.e., *CYP2A6*)

influences the likelihood of becoming nicotine dependent and the rate of progression in nicotine dependence among adolescents.^{21,22} However, these two studies differ in their findings, and it is not clear whether faster or slower nicotine metabolism confers risk for nicotine dependence. However, with regard to the nonspecific component of the risk path, studies have also linked polymorphisms in genes in the dopamine reward pathway to an increased likelihood of smoking progression,²³ greater smoking among male adolescents,²⁴ and a reduced likelihood of an adolescent being nicotine dependent.^{25,26}

Two genome-wide association studies have pointed to several novel genes that discriminated among adults who smoke regularly but did not become nicotine dependent and those who smoke regularly and became nicotine dependent.^{27,28} There appears to be some overlap between polymorphisms that distinguish individuals who became dependent on other substances from those who did not.²⁸ Likewise, a later candidate gene study found that the nicotinic receptor subunit gene *CHRNA5* distinguished between adults who smoke regularly but did not become nicotine dependent and those who smoke regularly and became nicotine dependent.²⁹ These findings have been replicated in five subsequent studies of adults.³⁰⁻³⁴ Studies also provide support for the importance of other nicotinic subunits identified in genome-wide association studies (e.g., *CHRNB3*).^{29,31,32} No studies were found that have prospectively evaluated the role of nicotine receptors in the emergence of nicotine dependence in adolescents.

Furthermore, a range of psychological and psychosocial moderators likely interplay with genetic vulnerability in regard to drug use, including smoking. For example, Dick and colleagues³⁵ reported that genetic effects on adolescent smoking were moderated by parenting behavior. The specific nature of

these interactive gene effects remains to be mapped with regard to the general and specific risk streams. However, initial clues are tantalizing. One study found that the dopamine receptor *D2 (DRD2)* gene interacts with other vulnerability factors, such as depression, to potentiate adolescent smoking progression.²³ In contrast, protective factors, such as team sport participation, appear to interact with genes in the dopamine reward pathway (i.e., *DRD2* and dopamine transporter *SLC6A3*) to prevent adolescent smoking progression.³⁶

Gene-by-gene interactions can also be considered. For example, genetic variation in the serotonin pathway (i.e., the short allele of the serotonin transporter *5-HTTLPR*) has been linked to increased smoking among adolescents.³⁷ However, a higher level of smoking was seen among girls who were homozygous for the long allele of *5-HTTLPR* and who lacked the dopamine receptor *DRD4*7-repeat* allele.³⁸ These two findings may reflect the moderating effects of one gene on another or possibly methodological differences between the studies.

Despite the recognition of these general outlines of the problem and these interesting initial genetic findings, it has proven difficult to identify candidate genes with replicable associations with adolescent smoking phenotypes; that is, several of the studies above disagree on the genotype that confers risk. As discussed in chapter 5, disparate findings may be partially explained by differences in study methodology and smoking phenotypes under investigation. At the same time, the methodological problems in identifying and measuring liability in those who have not yet initiated use are nontrivial.^{39,40} Endophenotypes in the context of prospective designs are a crucial tool in this regard.

Similar to most work in the field, the model discussed here assumes at least three inflection points leading to eventual

dependence, of which two (initiation and initial response) are covered in this chapter and one (persistence) is covered in chapter 9. It is assumed that genetic influences on these three inflection points are at least in part distinct. For one thing, it is likely that risks for initiation may fall partially into the general substance-use pathway and partially into a specific pathway involving attraction to nicotine, whereas a greater degree of drug-specific factors may be involved in initial response. However, initiation is an obvious prerequisite for progression and then dependence to emerge. In turn, numerous factors place an individual at risk for smoking initiation, progression to regular smoking, and nicotine dependence.⁴¹ Smoking obviously occurs in a psychosocial context in which nicotine availability is a necessary but not sufficient condition. Those psychosocial contexts are bypassed here so as to focus on avenues to understanding genetic predisposition to risk in the individual.

Candidate Neural Systems as Guides to Smoking and Nicotine-Dependence Risk Endophenotypes

In the temperament-based model, major circuits include the following: (1) A dopaminergic, appetitive, frontal-limbic circuit is related to approach behaviors, surgency, extraversion, novelty seeking, and impulsivity.⁴² It is well recognized that behaviors associated with these traits are related to drug-use risk generally,⁴³ so they are also relevant to smoking initiation risk. (2) A neural circuit anchored in amygdala and associated stress response circuitry is related to neuroticism, anxiety, stress response, fearfulness, and perhaps depression. These may include drug-specific as well as general risk characteristics inasmuch as nicotine may serve to relieve negative affect in a unique manner. (3) A frontal-thalamic-striatal circuit,

including dorsolateral prefrontal cortex and orbital prefrontal cortex, is related to effortful control, deliberative behavior, working memory, and neuropsychological executive functions. It is related to ADHD and inattention, and indirectly, to control of emotion. Additional neural and personality traits can be invoked to address hostility, as noted later.

Although this does not exhaust the neural mechanisms to be considered (in particular, those that are drug specific such as cholinergic systems in relation to nicotine use), they provide a starting point for organizing this list of behavioral and psychological markers that are likely to be part of a general risk pathway. They also provide a basis for bridging to more direct behavioral and cognitive probes of these same neural systems. What follows, therefore, outlines a multilevel-analysis perspective on key neural systems related to the behavioral markers above. In each case, an attempt is made to carry this out to the point of describing operational measures—that is, low-level experimental measures that can serve as endophenotypes for future studies.

Figure 8.1 outlines the basic conceptual framework as hypothetically linked to both behavioral and biological (i.e., central nervous system [CNS] and PNS) levels of analysis; potential linkages to other laboratory measures are noted here. This framework, presented in more detail in Nigg,⁴² draws on a handful of key formulations^{44–50} and is similar to a detailed presentation by Zuckerman.⁵¹ This perspective assumes a small set of reactive response systems and a regulatory/control system that comes under increasing volitional control with development. These systems underlie temperament and personality and are directly relevant to both psychopathology and self-control in children and adolescents. These systems are relevant to consideration of the general risk pathway;

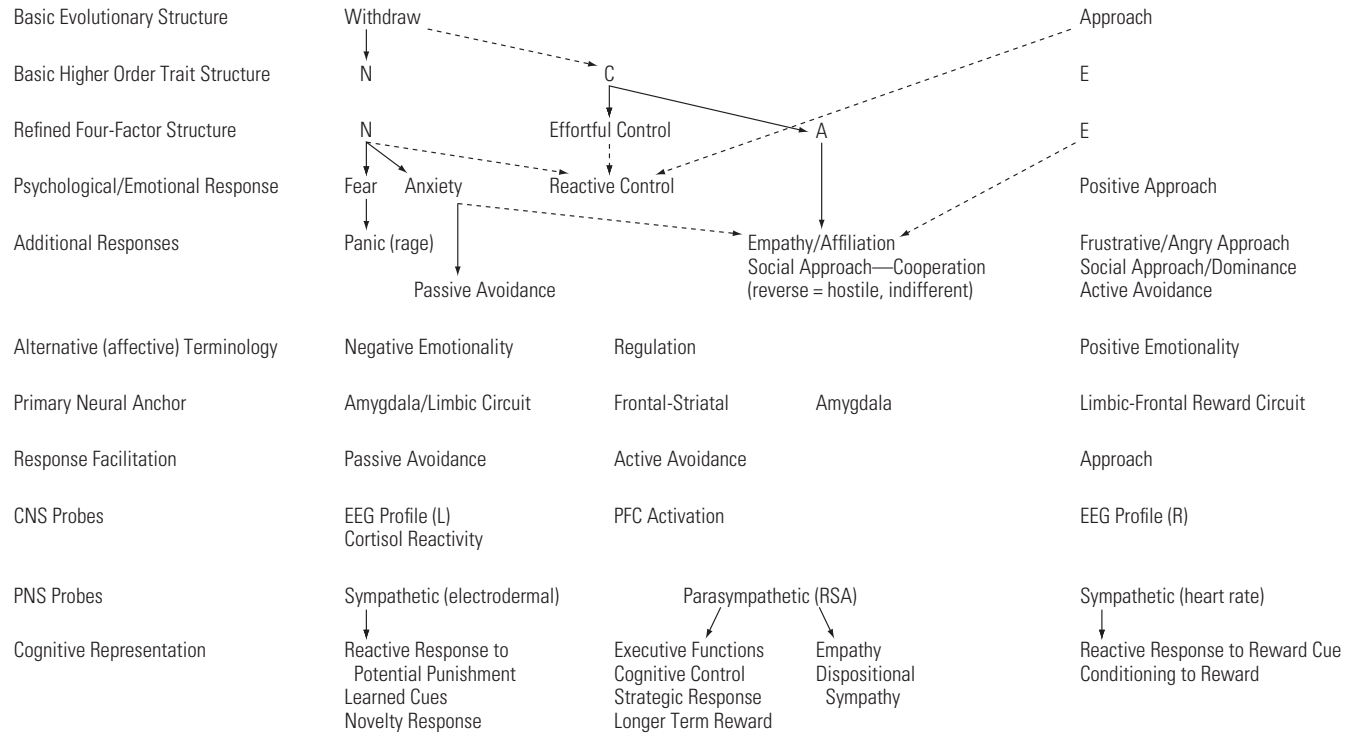
the degree to which they carry drug-specific risks will remain speculative here.

The behavioral traits are assumed to reflect a set of partially discrete neurobiological systems anchored at the level of the CNS in frontal-limbic neural networks and stress response systems and, at the PNS level, with reactivity of sympathetic and parasympathetic systems. Whereas the distinction between temperament and personality is debated in the field, that issue is bypassed here to focus on the conceptual behavioral and neural systems. The behavioral traits are known to be relatively stable across similar incentive conditions and to reflect reliable individual differences across development,^{52,53} although these effects are modest in size over long periods of time and include periods of substantial change in personality.⁵⁴ Yet, importantly, early trait scores, mediated by later trait scores, can predict onset of substance use.^{55,56}

The hierarchical framework begins with reactivity of two basic incentive systems—approach and avoidance⁴²—which are related to reactivity of autonomic as well as neural systems.⁴⁴ These are bottom-up systems. The framework then proceeds to top-down control, the ability to effortfully regulate responses as well as emotion and attention. Finally, all of these mechanisms influence attention and are moderated by arousal level.

Note again that the domains portrayed in figure 8.1 are of general importance to behavioral regulation; they are implicated in key psychopathologies (especially ADHD, conduct disorder, and mood disorders) and substance-use disorders as well as in risk factors for nicotine dependence. In the second half of this chapter, the focus is shifted to nicotine-specific processes. Therefore, the discussion begins here by outlining a conceptual neural model that will allow an organization of potential

Figure 8.1 Hierarchical Structural Model and Hypothesized Physiological Concomitants



Note. Adapted from Nigg, J. T. 2006. Temperament and developmental psychopathology. *Journal of Child Psychology and Psychiatry* 47 (3–4): 395–422; adapted from Beauchaine, T. P. 2001. Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. *Development and Psychopathology* 13 (2): 183–214; Calkins, S. D., and N. A. Fox. 2002. Self-regulatory processes in early personality development: A multilevel approach to the study of childhood social withdrawal and aggression. *Development and Psychopathology* 14 (3): 477–98; Markon, K. E., R. F. Krueger, and D. Watson. 2005. Delineating the structure of normal and abnormal personality: An integrative hierarchical approach. *Journal of Personality and Social Psychology* 88 (1): 139–57; Shiner, R., and A. Caspi. 2003. Personality differences in childhood and adolescence: Measurement, development, and consequences. *Journal of Child Psychology and Psychiatry* 44 (1): 2–32. Openness, associated with E, is omitted for simplicity. N = neuroticism, negative affectivity, withdrawal responding; E = extraversion, approach responding; C = constraint; A = affiliation/agreeableness; CNS = central nervous system; EEG = electroencephalographic; L = left; PFC = prefrontal cortex; R = right; PNS = peripheral nervous system; RSA = respiratory sinus arrhythmia.

endophenotypes, particularly those that may be nonspecific before exposure, and an analysis of previously studied risk factors at lower neurobiological levels, thus suggesting additional endophenotypes for consideration. Figure 8.2 provides an illustration of the potential links between genes, neurotransmitter activity and receptor function, endophenotypes for nicotine-dependence risk at or before initial nicotine exposure, and subsequent nicotine dependence.

Smoking Initiation and Progression Risk: Examination of Key Candidate Psychological Domains

A large literature base has linked adolescent smoking initiation and progression to several pre-occurring social, psychological, and behavioral factors. The smoking risk variables that are reviewed below are not exhaustive but reflect those most likely to be linked to potential genetic endophenotypes. For example, although peer smoking has consistently been shown to influence the likelihood of adolescent smoking initiation and progression,⁵⁷⁻⁵⁹ the underpinnings of peer behavior influence may more likely be environmental rather than genetic. Of course, parental smoking is a significant predictor of smoking initiation and progression.^{58,60-63} Clearly, the effects of parental smoking on adolescent smoking may be genetic and environmental, or may reflect gene-environment correlations, in that an adolescent both (1) inherits genotypes conferring smoking risk and (2) is in an environment in which smoking is modeled. Thus, no attempt is made to address all vulnerability to smoking and subsequent nicotine dependence; rather,

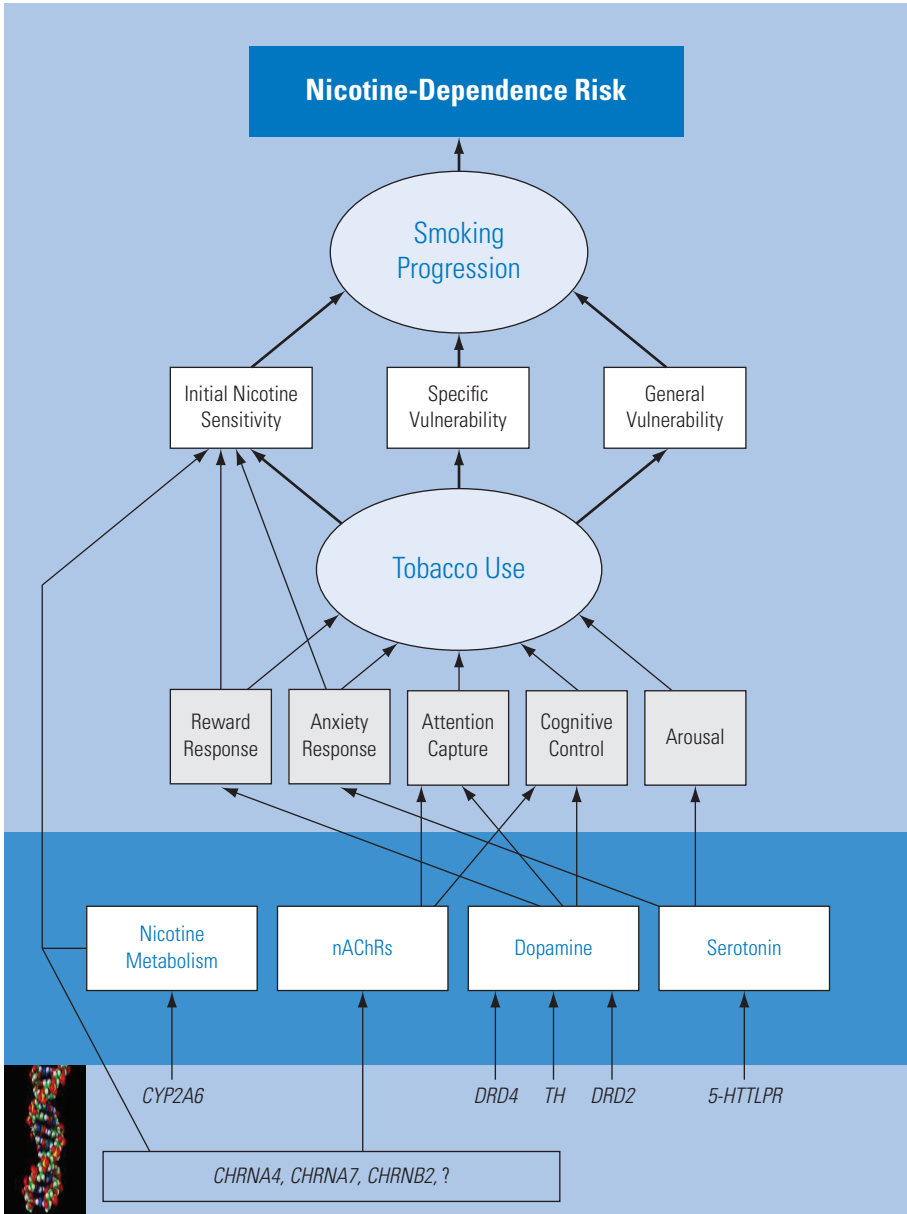
the focus is on potential markers of the genetic component of vulnerability.

In reading the sections on smoking risk variables, the reader should keep in mind that these factors themselves are complex phenotypes. They are framed here through the lens of a neurobiological temperament model that allows a multilevel analysis of these surface-level endophenotypes, perhaps bringing them closer to gene action. Each section that follows, therefore, begins at a “high,” or abstract, level of analysis with behavioral traits. It then proceeds to what is known about lower level, more molecular (i.e., either construct pure or single factor) laboratory measures. The laboratory measures can be viewed here as being genetically simpler and more promising as endophenotypes than are the trait measures. However, whether this is always true about these measures remains an empirical question in nearly every case. The purpose here is to show the linkages across these levels of analysis to assist the field in conceptualizing endophenotypes as target measures. This is illustrated by analyzing the most-well-studied molecular measures and by suggesting logical, additional measures of the same systems that are essentially unstudied in relation to smoking vulnerability.

Approach-Related Risk Variables: High-Level Psychological Traits

The neural incentive system, labeled here as “approach,” is associated with psychological processes, such as willingness to approach possible incentive or reward/reinforcement, and with speed of reinforcement learning. It is related also to the personality traits of impulsivity and novelty seeking as well as extraversion^{64,65}—all of which are among the surface traits that have been linked to smoking risk. Extraversion, the most abstract of these traits, includes

Figure 8.2 Example of How Potential Endophenotypes Can Link Genes to Nicotine-Dependence Risk at or before Initial Nicotine Exposure



Note. Endophenotype areas are presented in gray squares. Specific and general vulnerability paths are recognized. 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. nAChRs = nicotinic acetylcholine receptors.

several lower order constituent traits such as positive emotionality, sociability, and activity level.⁴⁹ An extensive literature documents both the reliability of individual differences in children and adolescents on these dimensions and the fact that they cohere in a superordinate factor at least by early childhood (for reviews see Calkins and Fox;⁴⁵ Putnam and colleagues;⁶⁶ Rothbart and Bates;⁴⁸ and Shiner and Caspi⁴⁹), although some developmental change may emerge with regard to the lower order traits contributing to extraversion.⁵² Disagreement remains as to the neurobiological core element of this supertrait (see Depue and Collins⁶⁷ and accompanying commentaries). However, to facilitate neurobiological and cross-species analysis of smoking risk endophenotypes, extraversion is conceptualized here as related at the level of the CNS to the appetitive, dopaminergic systems, including the nucleus accumbens and ascending frontal-limbic dopaminergic networks.^{42,64,65} At the level of the PNS, extraversion is related to sympathetic activation, with one index being heart rate acceleration following the application of effort or the appearance of incentive.^{44,68} These CNS and PNS measures then become operational candidate endophenotypes that may be closer to gene action than are surface traits such as extraversion or novelty seeking.

Impulsivity

Impulsivity is used here to mean the tendency to act without adequate preparation or thought or to act hastily in contexts that call for a slow, careful response. One common way to operationalize impulsivity is via delay discounting. “Delay discounting,” a concept found in behavior economic theory, among other literatures, describes the process in which the value of a reward is discounted as a function of delay to its delivery.⁶⁹ Like other impulsive subjects, smokers tend to discount the value of future

reinforcers more than do nonsmokers.^{70,71} Thus, impulsivity, seen as a tendency to choose reward immediacy over reward magnitude,^{70,72} is a risk factor for smoking. Delay discounting rates have been shown to correlate with impulsivity, age at first substance use, and substance use.^{72–75} Delay discounting affects the type of reinforcers that adolescents choose over time⁷⁶ and appears to involve two separate neural systems.⁷⁷ However, a key component of neural support for delay weighting involves ascending midbrain dopamine circuits. Thus, genes and measures tapping these circuits are likely to be of interest.

Novelty-Seeking Personality

Novelty seeking is characterized by a tendency to seek out new and exciting stimuli; engage in sensation-seeking, impulsive, and risk-taking behavior; and to be sensitive to reward.^{78–80} This personality dimension predicts tobacco use during adolescence^{81,82} and early onset of smoking in adolescent boys.⁸³ Indeed, a study of longitudinal smoking patterns from ages 14 to 18 years found that adolescents high in novelty seeking were about 15%–20% more likely to be members of a trajectory involving regular smoking than of a never-smoking trajectory.⁸⁴

Adolescents high in novelty seeking also tend to be more receptive to tobacco advertising, which, in turn, has been linked to smoking progression.^{85,86} The heightened receptivity to tobacco advertising among youth high in novelty seeking may be attributable to their greater need for stimulation and rewarding experiences. Structural equation models suggest that novelty seeking indirectly affects substance use through other variables that are more proximal to use.^{82,87} This might especially be the case for cigarette smoking.⁸⁸ Evidence also suggests that exposure to novelty activates the same neural structures that mediate the rewarding effects of substances

of abuse.⁸⁹ Thus, like impulsivity, individual variability in novelty-seeking and drug-seeking behaviors may be related to individual differences in the dopamine reward pathway.^{90,91}

Extraversion

Extraversion is characterized as an outgoing, sociable, energetic disposition. Data suggest that extraversion is associated with smoking initiation among adolescents⁹² as well as current smoking status.^{93–95} A later study found that higher levels of extraversion increased the odds of initiating smoking by about 40%.⁹² Extraversion appears to have direct and indirect effects on adolescent smoking progression.⁹⁶ Extraversion is a multidimensional trait that has several alternative formulations. However, one major psychobiological formulation is that it pertains to the approach system—that is, the same ascending dopamine circuitry involved in motivation and reinforcement response noted above.

Approach: Neural Analysis and Laboratory-Based Endophenotype Measures

The appetitive, or approach, system, involving the midbrain or mesolimbic dopamine circuitry (including the nucleus accumbens) is central here. Experimental probes typically involve examining differential response to (1) anticipated and (2) actual reward versus control or baseline responding. (“Reward” here refers to the reinforcing substance, or object of the goal-directed behavior, not to the hedonic response to smoking or nicotine discussed later in this chapter and in chapter 9.) Tasks of this nature can then be examined behaviorally (e.g., changes in reaction time), physiologically (in particular, changes in heart rate), and neurobiologically (in particular, changes in activation in nucleus accumbens via neuroimaging).^{97,98}

Nearly all of these types of tasks have been experimentally designed in a nonstandard manner across different laboratories, so their reliability and heritability are poorly assessed. However, what is known about key candidate measures is highlighted here.

Reinforcement Response

Reinforcement response is related to cognitive control in that (1) the two processes are mutually modulating and (2) ascending dopaminergic circuits are also important in reinforcement response. Relevant brain structures again include prefrontal cortex, as well as limbic-striatal structures, perhaps most notably the nucleus accumbens (which activates for potential reward [a signal reinforcer] as well as actual reward). Here, several angles on the reinforcement response system are considered. First, this system is responsible for learning associations that are meaningful. This learning (e.g., correlational learning or associative learning) is poorly studied in youth who go on to smoke. Second, the system is responsible for learning associations with predictors for reward (operant learning), and similarly, for extinguishing response to operant predictors that are no longer linked to the reward or reinforcer. Third, one can ask about the weight put on a potential reward (as opposed to an actual reward; here the interest is in the signal stimulus). A highly active ascending dopamine circuitry in the approach circuit is expected to place high value on signal of potential reward.⁹⁹ One can then ask about weighting of immediate, small reward versus later, larger reward, or delay discounting. Steep delay discounting is related to impulsive behavior and may be related to differences in this reinforcement system. This last perspective on reinforcement response is the only one that has been studied as of 2008 in relation to smoking onset, so it is focused on here via the following key tasks.

Reward Signaling and Discounting Tasks

Reward signaling in the brain involves several discrete elements⁹⁹ that will be useful to decompose in future studies of reward and smoking risk. The properties of nearly all tasks are still being worked out. However, several promising probes that could serve as endophenotypes for future research have emerged, such as the Iowa gambling task.¹⁰⁰ This task is the one most often used in substance-use research to assess reward weighting and is associated with alcohol and drug abuse.¹⁰¹ As of 2008, it has not yet been utilized to assess risk for smoking onset. In this task, the individual “plays” a series of cards from four decks. Each deck has a different reward-cost ratio. Impulsive individuals tend to choose big rewards even though they come with bigger losses (and a net loss in the end) instead of smaller rewards that lead to a net gain. The biological linkage to this task of brain regions for the ascending dopamine circuitry described previously is supported by lesion.¹⁰⁰ Another related paradigm is reward signaling. In this task, the youth sees a cue indicating that a reward of varying size will soon be received. The cue appears to activate the nucleus accumbens.⁹⁷ In one small study, failure of such activation was related to ADHD.⁹⁸ Reward signaling has promise but has not been studied genetically.

Reward-discounting tasks may be the most promising; these are used with either real or hypothetical rewards, with similar effects,¹⁰² and tasks using real rewards can be adapted for very young children.¹⁰³ Most well studied is a hypothetical reward-discounting task, which can be useful beginning as early as middle childhood. In this task, the youth makes a series of hypothetical choices indicating a preference for a larger amount of money later (e.g., \$100) and a smaller amount now (e.g., \$10), with the amounts stochastically varied to find that individual’s breakpoint of preferring to wait. This

task has the advantage of being directly transferable to animal studies, a major advantage for an endophenotype. As a result, linkages to reward circuitry in ventral and orbitofrontal cortex and ventral striatum/nucleus accumbens have been demonstrated in animal research¹⁰⁴ and in human neuroimaging studies.¹⁰⁵ Further, behavior on this task is related to ADHD,¹⁰⁶ which is one behavioral risk factor for smoking.

In fact, considering predictive validity, these types of measures are not well utilized with regard to risk of nicotine use initiation or, for that matter, much studied in relation to children. The majority of studies of delay discounting have involved adult populations or those who are already smoking (chapter 9), whereas most studies of reward cue response tasks have not looked at smoking outcomes in youth. However, current smokers tend to discount the value of future rewards compared to never smokers and those who do not smoke daily or regularly (e.g., chippers).^{102,107} It is, therefore, unclear if reward discounting reflects propensity to become addicted once exposed to cigarettes or reflects risk for onset.¹⁰² Further, the role of this variable in adolescent smoking has either been unclear or indirect.^{84,108} For example, one study found that delay discounting (based on a self-report measure) was indirectly related to smoking initiation and progression through variables more proximal to smoking.⁷⁶ Data related to adolescent smoking cessation indicated that adolescents unable to achieve abstinence discounted monetary rewards on a computerized discounting task more than did those adolescents who were abstinent from smoking.¹⁰⁹ Finally, laboratory studies of adult smokers (smoking ≥ 15 cigarettes daily) suggest that upon abstinence, regular smokers experience abstinence-associated deficits in incentive motivation.¹¹⁰ For example, compared to performance during an abstinence phase, smokers show increased responsiveness to monetary reward on the Card Arranging Reward

Responsivity Objective Test during a nicotine phase.¹¹⁰

With regard to heritability, these tasks are not well studied. One small twin study suggested that heritability of delay aversion in young children is quite low, on the order of .2 to .3,¹¹¹ suggesting that unless its genetic architecture is very simple, it will not be a useful endophenotype. However, it may be that either latent variables that resolve measurement unreliability will yield a stronger genetic signal in this domain or that delay discounting tasks will exhibit higher heritability.

Physiological Measures of Reward Response

In addition, this system can be measured either peripherally by heart rate acceleration to a possible reward or centrally by functional magnetic resonance imaging (fMRI) measures of nucleus accumbens activation to potential reward.⁹⁷ These measures have extensive validation literature, suggesting they tap the relevant reward circuitry,^{97,112} but virtually no heritability studies.

Avoidance-Related Risk Variables: High-Level Psychological Traits

Neuroticism

Neuroticism, a basic, higher-order personality trait, reflects a generalized tendency to experience negative affect, to have difficulty coping with stress, and to be nonresilient in the face of change. It has substantial heritability.^{113–115} High neuroticism has been shown to prospectively predict smoking behavior in adolescents and young adults.^{116–118} These studies of neuroticism and youth smoking acquisition appear to be consistent with a large body of adult research showing a positive association

between neuroticism and smoking.¹¹³ Later findings indicate a significant association between platelet monoamine oxidase (MAO) activity and neuroticism,⁶⁹ which are both associated with smoking behavior.¹¹⁹ About 10% of the genetic variation in neuroticism appears to be due to genes that also act on MAO. MAO activity has been shown to increase as a result of smoking and to decrease during periods of smoking cessation.^{120,121} Thus, genes related to MAO activity and their biological markers may be useful targets for genetic research on smoking risk.

Stress

Related, and often considered within the overall construct of neuroticism, are the subjective feelings of stress. There has been less research on the impact of subjective feelings of stress on adolescent smoking acquisition than on other psychological variables. The available research, however, suggests that stress is related to smoking initiation,^{116,122} smoking status,^{123–125} and a decreased likelihood of quitting¹²⁶ in adolescents. Yet, an important and often overlooked aspect of this link between stress and smoking is that it appears to act in only one direction. Controlled studies in adults confirm that acute stressful challenges, for example, reliably increase smoking behavior, but that an increase in smoking does not seem to subsequently relieve the subjective distress resulting from the challenges,¹²⁷ although such smoking clearly relieves distress due to tobacco abstinence.¹²⁸ It is not at all clear that stress relief explains the reliable increase in smoking due to all or even most stressors.

Depression

Depression is one of the most common psychiatric disorders in adolescence. It is characterized by depressed mood, anhedonia, vegetative symptoms, and impaired psychosocial functioning.

Subthreshold depression (depression that does not meet all criteria for the diagnoses of major depression) is also prevalent in youth; it is associated with psychosocial impairment and often precedes and follows a major depressive episode.^{129–135} Neuroticism is a major diathesis for depression.¹³⁶ Depression predicts smoking initiation,^{137,138} current smoking,^{139,140} and nicotine dependence in adolescents.¹⁴¹ About 32% of adolescent smokers have a lifetime history of major depression compared to 17% of nonsmokers.¹⁴² Major depression is associated with a 19% increase in the average daily smoking rate (cigarette intake) and a 75% increase in the odds of being nicotine dependent from mid-adolescence to young adulthood (16–21 years old).¹⁴³ Young adults (aged 21–30 years) with a history of major depression are three times more likely to progress to daily smoking compared to those without major depression¹⁴⁴ and over two times more likely to progress to nicotine dependence.¹⁴⁵

Some research suggests that the association between smoking and depression results from common factors (e.g., genetic or environmental factors) that are associated with both increased risks of depression and increased risks of smoking.^{146,147} Significant comorbidity between smoking and major depressive disorder was found before, but not after, adjustment for presence of other psychiatric disorders.^{142,148} Other studies of adolescents and adults suggest that control for factors common to smoking and depression was not adequate to explain their association.^{143,145,149,150} Alternatively, the association between smoking and depression may reflect a cause-and-effect relationship. The direction of the causal effect is controversial.^{58,138,140,142,144,151}

Thus, highlighting concerns with heterogeneity in risk pathways to smoking, some findings indicate subpopulations of adolescents who differ with respect to the relationship between smoking

and depression (i.e., smoking increases depression symptoms in some and decreases depression in others). Specifically, the study empirically identified three distinct depression trajectories from ages 14 to 18 years. Smoking was not associated with being in the low symptoms trajectory but was associated with acceleration in depressive symptoms for adolescents in the moderate symptoms trajectory and with a deceleration of depressive symptoms in the high symptoms trajectory.¹⁵² Thus, a subgroup may exist (those with higher symptoms) who “self-medicate” depressive symptoms with nicotine. A later section considers whether this is a direct effect or an indirect effect mediated by the improved attention provided by the nicotine.¹⁵³

Another study found that cigarette smoking had disproportionate reward value for depressed smokers.¹⁵⁴ It is possible that the heightened reinforcing value of smoking may mediate the relationship between depression and smoking behavior. The mesocorticolimbic dopamine reward pathway appears to be dysfunctional in individuals with major depression, such that they are more responsive to substances that activate these reward systems.^{155,156} Within a tripartite neurobiological model,^{157,158} depression is viewed as reflecting both an elevated neuroticism, which is a nonspecific marker of internalizing psychopathology, as well as a shortage of positive affect (underfunctioning of an approach system). Thus, a key question for smoking endophenotypes is whether smoking risk is associated with over- or underfunctioning of the incentive reward systems in the brain. Multiple genetic pathways are possible in this regard.

Anxiety

Like depression, anxiety disorders can range in degree from a full-scale disorder to subthreshold levels.¹⁵⁹ Anxiety tends to be linked to neuroticism and to negative affect.¹⁵⁷ The hallmark features of anxiety

disorders include uncontrollable worry, physical symptoms such as sweating palms and increased heart rate, and secondary features such as restlessness and difficulty concentrating.¹⁵⁹ Research suggests an association between cigarette smoking and/or nicotine dependence and anxiety disorders in young adults and adolescents.^{149,160–162} However, it appears that smoking may precede the onset of anxiety disorders.^{160,163} In fact, adolescents who smoked more than 20 cigarettes a day were 6.8 times, 5.5 times, and 15.9 times more likely to be diagnosed with agoraphobia, generalized anxiety disorder, and panic disorder, respectively.¹⁶³ Anxiety disorders during adolescence were not associated with cigarette smoking during young adulthood. In contrast, another study found that anxiety symptoms predicted smoking initiation in youth.¹³⁸ Chronic symptoms of anxiety during adolescence predicted progression to nicotine dependence during young adulthood.¹⁶⁴ In addition, adolescents and young adults with social fears have an increased risk of nicotine dependence.¹⁶⁵ Thus, the relationship between anxiety and smoking may depend on the degree of anxiety (clinical diagnosis versus subclinical symptomatology) as well as the type of anxiety disorder.

Alternatively, the relationship between smoking and specific anxiety disorders may not be best represented by a direct effect. Neuroticism predicts the co-occurrence of smoking and panic disorder¹⁶⁶ and moderates the effects of maximum smoking rate on lifetime history of panic disorder.¹⁶⁷ Indeed, it has been argued that mediator and moderator approaches that consider contextual factors may be more informative than direct-effect approaches for understanding the relationship between negative affective states, such as anxiety, and the smoking behavior developmental continuum.¹⁶⁸

Neurobiologically, anxiety, and its emotional cousin, fear, are related to activation of

the particular nuclei in the amygdala and associated neural structures that signal potential negative events.^{169,170} MAO plays a significant role in serotonin metabolism and transmission,^{171,172} which has been implicated in anxiety disorders.¹⁷³ Models that consider the links between MAO, serotonin, and smoking may advance understanding the relationship between anxiety and smoking behavior from a genetic perspective.

Avoidance: Neural Analysis and Laboratory-Based Endophenotype Measures

The avoidance dimension, as conceptualized here, is anchored by readiness of behavioral withdrawal-related behavior in potentially unrewarding or uncertain contexts, and with associated affective reactivity (i.e., fear, anxiety, and sadness). This dimension is related to emotions of anxiety and depression, as well as to the personality trait of neuroticism, which, as noted above, is another set of surface traits related to smoking risk. Neuroticism is the most abstract of these and has component factors such as negative affectivity and anxiety. As discussed in the previous section, neuroticism can be viewed at lower levels of analysis that may be closer to gene action. In this case, the reactivity of these avoidance responses is related at the level of the CNS to limbic-frontal neural circuitry and the amygdala. Depue and Lenzenweger¹⁷⁴ describe fear as an immediate threat response involving short-term activation in the central amygdala nucleus, whereas anxiety is a long-term activation to low-grade threat associated with activation in the bed nucleus of the stria terminalis in the extended amygdala. Thus, reactivity of a stress-response or danger-alarm system (hypothalamic-pituitary-adrenocortical [HPA]) axis and associated autonomic and hormonal effects, which at the CNS level includes the lateral hypothalamus, reticular formation, and other structures) is a key

feature. At the level of the PNS, reactivity of this set of response systems is hypothesized to emanate in sympathetic activation of autonomic systems, in particular electrodermal skin response to anticipated loss of reward.^{44,112} At the CNS level, as noted in table 8.1, electroencephalogram (EEG) measures appear to index relative degree of predisposition to approach and avoidance activation by characteristic lateralized asymmetries in EEG power.^{45,175–178} The fMRI data suggest that amygdala activation (associated with avoidance of potentially unpleasant events) and nucleus accumbens activation (related to approaching a potentially positive event) appear to be mutually inhibiting responses.¹⁷⁹ Examination of these types of physiological measures as potential endophenotypes may bring data closer to gene action and help identify risk mechanisms for smoking beyond the broad surface trait of neuroticism or its constituent elements of anxiety or negative mood. However, only a handful of such measures have been examined, as noted in table 8.1.

Neuroendocrine Response to Stress/Cortisol

In particular, neuroendocrine response in relation to danger and stress response systems, as potential reflection of avoidance-related responding,^{174,181,182} includes two biological systems (conceptually related respectively to psychological fear and anxiety, as distinguished in the previous paragraph). First, the sympathetic adrenomedullary system is thought to be a fast-acting system (including providing adrenalin for “emergency” or alarm response) that in day-to-day regulation of behavior may index excitement, vigilance, or alertness; however, another interpretation is that it indexes the negative affectivity “fear” response.¹⁷⁴ Second, the limbic HPA system is thought to be a slow-acting stress response system associated with arousability and negative emotions¹⁸¹—more specifically, anxiety.^{174,183}

Its activity (primarily, corticotrophin-releasing hormone) is most often indexed by peripheral cortisol levels. Set points or reactivity in these systems may underlie the observed personality correlates of smoking risk (e.g., smoking to alleviate fear or anxiety, or attentional bias toward drugs of opportunity to relieve internal emotional discomfort). Therefore, cortisol reactivity is a candidate endophenotype that may capture predispositions to smoking, albeit nonspecifically, at a lower level of analysis neurobiologically. However, its promise is somewhat unclear. Associations of cortisol measures with behavioral measures are decidedly mixed,¹⁷⁶ due in part to the need to interpret cortisol (and for that matter, other biological markers) in relation to behavioral context.^{44,182} Therefore, it may be useful to examine cortisol reactivity in relation to smoking cues or in relation to stressors that are contextually linked to smoking onset. Yet, the decline in cortisol soon after quitting is predictive of quitting success in chronic smokers, as noted in chapter 9, suggesting a very different process indexed by cortisol in that population.

Other Measures

Further measures could be considered. These include skin conductance response and heart rate to potential loss of reward, as well as other measures of avoidance learning.¹¹²

Control-Related Risk Variables: High-Level Psychological Traits

Attention Deficit Hyperactivity Disorder

ADHD is a developmental disorder characterized by age-inappropriate levels of hyperactivity and impulsivity and an inability to sustain directed attention.¹⁸⁴ Because of its very high heritability, early onset (generally much earlier than smoking initiation), and long-term stability of

Table 8.1 Extant Data on Potential Endophenotypes and Their Measurement

Neural system/function	Reliability	Heritability	Validity
Attentional capture			
Orienting and alerting tasks	Unknown	Unknown	NA
Flanker task	Moderate	Low	NA
Posterior activation on fMRI	Unknown	Unknown	NA
N1 ERP component	Moderate	Moderate	NA
P2 ERP component	Moderate	Moderate	NA
Arousal			
EEG slow-wave activity	High	High	NA
Reaction time	High	Moderate	NA
Signal detection	Moderate	Unknown	NA
Cognitive control/top-down attention			
Stroop interference task	Moderate to low	Poor	NA
Working memory tasks			
Digit span backwards	Moderate to high	Unknown	NA
N-back	Unknown	Unknown	NA
Spatial span back	Unknown	Unknown	NA
Response inhibition			
Stop-go task	High	Moderate	NA
Go/no-go task	Moderate	Moderate	NA
Antisaccade task	Moderate	Unknown	NA
Cardiac measures			
Vagal tone/RSA	High	Unknown	NA
CNS measures			
P300 amplitude	High	Mod to high	1
Executive functioning/planning			
Tower of London	Poor	Unknown	NA
Tower of Hanoi	Poor to mod		NA
Trait measures			
Personality constraint	High	Mod to high	NA
Effortful control	High	Moderate	NA
Approach-related and reward response markers			
Iowa gambling task	NA	NA	NA
Delay discounting task	High	Poor	1
Incentive response reaction time	NA	NA	NA
Cardiac measures			
Heart rate acceleration to possible reward	NA	NA	NA
CNS	NA	NA	NA
Nucleus accumbens activation	NA	NA	NA
Trait measures			
Extraversion	High	Mod to high	2
Positive affectivity	High	Moderate	NA
Anxiety response and avoidance-related measures			
Response cost measures			
PNS			
Skin conductance	Moderate	Poor ¹⁶⁰	NA
Heart rate to loss of reward	NA	NA	NA
CNS			
Lateralized EEG profile	NA	Mod to high	NA
Trait measures			
Neuroticism	High	Mod to high	2
Negative affectivity	High	Mod to high	NA

Note. For reliability, high = $\geq .7$, moderate = $.5-.7$, poor = $\leq .5$; for heritability, high = $.5-.7$, moderate = $.3-.5$, low = $\leq .3$. See text for biological plausibility and references. Predictive validity pertains only to smoking onset, not to other outcomes. In that respect, validity here is rated as follows: 1 = little supportive data; 2 = moderate amount of supportive data; 3 = well established. Heritability data are provided in the text; see corresponding sections in the text for review of literature and citations relevant to the conclusions stated in this table. NA = data are too sparse to enable any comment or studies are not available in this domain to insert a rating; fMRI = functional magnetic resonance imaging; ERP = event-related potential; EEG = electroencephalogram; mod = moderate; RSA = respiratory sinus arrhythmia; CNS = central nervous system; PNS = peripheral nervous system.

symptom levels (though not of diagnostic type),^{185,186} it has some advantages over later-onset disorders (such as anxiety and depression) in potentially predicting smoking onset.

The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (*DSM-IV*)¹⁵⁹ identifies three subtypes of ADHD: predominantly inattentive, predominantly hyperactive and impulsive, and combined, although the appropriate etiological subtyping of ADHD and characterization of its own cognitive endophenotypes remain an active area of investigation.^{187,188} ADHD has been associated with an increased risk of adolescent smoking initiation and progression.^{189–196} Youth diagnosed with ADHD and youth with higher ADHD symptoms (although not a diagnosis) tend to start smoking earlier than those without either.^{192,193,197,198} ADHD history also predicts inability to quit among dependent smokers, as discussed in chapter 9.

It is unclear whether inattention or hyperactivity/impulsivity are equally predictive of smoking or whether one set of symptoms is more strongly associated with smoking than the other. This is important because some models suggest that symptoms of inattention may yield partially distinct temperamental and neural correlates (primarily related to cognitive control) versus hyperactivity/impulsivity (primarily related to reward response).¹⁸⁸ Adolescent and adult research supports an association between smoking and inattention, but not between smoking and hyperactivity.^{195,199} It has been speculated that those with ADHD may smoke to self-medicate their attentional deficits.²⁰⁰ In support of this notion, Molina and Pelham¹⁹³ found inattention rather than hyperactivity/impulsivity to be more predictive of subsequent smoking. However, retrospective reports of childhood ADHD symptoms among young adults suggests that hyperactivity/impulsivity is a stronger

predictor of regular smoking than are ADHD inattention symptoms.¹⁹⁷ Laboratory-based research has found that acute nicotine administration positively affects both cognitive and behavioral inhibition among nonsmoking adolescents with ADHD,²⁰¹ but both of these may be related to cognitive control and inattention symptoms.¹⁸⁷

However, many studies did not adequately control for conduct problems/conduct disorder. These antisocial behavior problems often overlap with ADHD and may identify the subgroup at greatest risk of smoking. The association between ADHD and adolescent substance use, including smoking, is often weakened or rendered insignificant when comorbid conduct disorder is considered,^{200,202–204} although not in all studies,^{153,203,205} especially when the independent effects of inattention are evaluated.²⁰³ Some data suggest that ADHD and conduct disorder may be associated with different substance-use characteristics, such as early onset and frequency of use.²⁰⁶

Neurobiologically, ADHD, and particularly the inattention component, is thought to be related to deficits in cognitive control that are instantiated in the prefrontal cortex, striatum, and cerebellum. These frontal-subcortical circuits are involved in working memory, cognitive control, and planning and execution of complex behaviors. Laboratory measures of these abilities are well associated with ADHD²⁰⁷ and, therefore, may be potential laboratory-based candidate endophenotypes for smoking onset. ADHD has been reliably associated with a handful of specific genes, including the dopamine transporter gene, dopamine *D4* receptor gene, and others,²⁰⁸ potentially providing further clues to the genetics of smoking initiation risk. An additional neurobiological aspect of ADHD is apparent association with low cortical arousal, as indicated by poor signal detection²⁰⁹ and excess slow-wave EEG.²¹⁰ Also consistent with arousal dysregulation as a risk phenotype, Wong and

colleagues²¹¹ found that sleep problems of three- to five-year-olds, as rated by mothers, predicted early drug-use onset, including smoking by 14 years of age, in adolescence. Whether smoking provides specific compensation and is uniquely related to the underaroused profile described above is unclear, but as noted, this is one possible way of understanding smoking attraction in these youth. Endophenotypes that tap an arousal system, particularly ascending noradrenergic circuits, may therefore be of use.

Conduct Disorder and Aggression/Hostility

Conduct disorder is defined as a persistent pattern of behavior in which age-appropriate societal norms are repeatedly violated.¹⁵⁹

Typical behaviors include aggression, deceit, stealing, damage to others property, cruelty, and general rule violations. Adolescents with conduct disorder are almost 13 times more likely to be current smokers than are adolescents without conduct disorder.²¹²

In fact, conduct disorder predicts earlier, regular (daily) adolescent cigarette smoking and has been shown to be a mechanism by which family risk factors affect adolescent smoking.¹⁸⁹ Externalizing disorders, such as conduct disorder, tend to have the highest associations with progression to daily smoking and nicotine dependence compared with other psychiatric disorders.¹⁹⁴ At the same time, they are clearly recognized as a general risk factor for drug use overall and are not specific to nicotine use.^{9,43,213}

A later study found that physical aggression increased the odds of smoking before 14 years of age by 16%. Thus, adolescents with earlier onset of smoking tend to be more physically aggressive than those who have not initiated smoking by this age.⁸⁵ It is possible that adolescents who have difficulty coping with anger and frustration use cigarettes as a coping method. Nicotine has been shown to have palliative effects on anger and to reduce the frequency of

anger reports in smokers with high levels of hostility.^{214,215} In fact, research that evaluated the metabolic effects of nicotine in the brain found that nicotine triggered dramatic changes in regions of the brain important in behavioral control in individuals rated as more aggressive or easier to anger.²¹⁶ This may be especially relevant for understanding adolescent smoking in that adolescents attempt to manage extremes in emotion before behavioral control centers in the brain have finished maturation.²¹⁷ Animal models indicate that aggressiveness may be partially due to fetal nicotine exposure; for example, rodents exposed to nicotine in utero had higher levels of aggressive behavior compared to those with no in utero nicotine exposure.

However, the developmental progression requires further elucidation. Most youth with conduct disorder had earlier oppositional defiant disorder,²¹⁸ and in turn, youth with oppositional defiant disorder tend to have irritable early temperament.²¹⁹ Irritable temperament may reflect perinatal risks, including prenatal exposure to nicotine,²²⁰ or genetic effects on regulation of negative affect/irritability. Likewise, ADHD is a risk factor for later development of conduct disorder.²¹⁹ It may be that these represent related routes of vulnerability, with smoking onset as a later outcome of these early risks. Identifying endophenotypes related to conduct disorder will therefore overlap with endophenotypes related to ADHD. Indeed, studies suggest that conduct disorder, ADHD, and substance use may be explained by a highly heritable latent phenotype of behavioral disinhibition.²²¹

Control: Neural Analysis and Laboratory-Based Endophenotype Measures

Previously, two superordinate dimensions were noted: (1) extraversion and (2) negative emotionality, or neuroticism.

The third superordinate dimension in personality structure is variously labeled as low constraint,²²² unsocialized sensation seeking,⁵¹ and low effortful control.^{48,223} Higher levels of constraint and effortful control are inversely related to ADHD (see Nigg¹⁸⁷ for a review) as well as to a lesser extent with aspects of conduct disorder and impulsive aggression. When dysfunctional, it is related to difficulty in regulating attention and may be related to ease with which attention can be captured by incentives or potential incentives in the environment (e.g., possibility of trying drugs or cigarettes). “Effortful control in young children,” as defined by Rothbart and colleagues (e.g., see Putnam and colleagues⁶⁶) includes elements of attentional control, low-intensity pleasure, and attentional shifting and focusing behaviors. Again, these surface behaviors can be analyzed at a neurobiological level that may suggest candidate endophenotypes.

The capacity for and tendency to exert effortful control is theorized to depend on anterior neural systems. These neural systems emphasize frontal-striatal neural loops that are dopaminergically modulated.²²⁴ This system can regulate the affective response systems. For example, human neuroimaging studies have now shown a role for top-down prefrontal modulation of subcortical regions.^{225,226} In other words, prefrontal activation is associated with reduced limbic activation. The importance of this is that it provides imaging evidence confirming the direct neural regulation of affective response by top-down effortful control. If weakness in the top-down control system is associated with smoking risk, future smokers would be expected to show weaker prefrontal activation on the types of challenge tasks used in these studies.

Cognitive control is a more formal term for effortful control. It refers to the ability to manage competing information and

deliberately direct attention in the service of task demands. It includes subsidiary abilities such as response suppression, working memory, and response selection. From this angle, numerous available laboratory measures can be identified that may be viable endophenotypes. These are extensively validated by neuroimaging data as activating the neural circuits of interest (described in sections below). These measures tend to involve circuitry modulated by dopamine and noradrenergic activity. In turn, acetylcholine neurons likely modulate these circuits.²²⁷ They, therefore, are relevant to nicotine maintenance as well as onset. The endophenotypic criteria (reliability, heritability, and predictive validity) are described and considered below for selected measures of cognitive control, identified by their having some data on association with smoking onset and/or maintenance. Again, if weak cognitive control is associated with vulnerability to smoking onset, adolescents who go on to smoke would be expected to have slower reaction times and more errors on executive function tasks than do adolescents who do not go on to smoke. Also, these cognitive-control abilities are important to academic success; if nicotine improves these abilities, then that improvement could add to nicotine’s reinforcing effects, as discussed in the next section. For example, it may be that nicotine acutely enhances cognitive control.²²⁷

Response Inhibition

Response inhibition is the ability to suppress a prepared response in a rapid-decision context. Several widely used tasks have been used to assess it. The go/no-go task is the most well known. The individual presses a key as rapidly as possible when the target appears (e.g., the letter “X” appears at variable intervals averaging once per second on the computer screen). On a minority of trials (25%), the “X” is colored red, or a different letter appears, meaning it is a

“no-go” trial. Another task is the antisaccade task in which individuals are to refrain from moving their eyes toward a target that suddenly appears in the periphery of their vision; that is, they must suppress the reflex to move toward that target and, instead, move their eyes in the opposite direction to get a correct response. Perhaps the most-well-validated measure of the ability to suppress a prepared response is the stop-go task.²²⁸ The individual faces a computer screen and on a series of trials decides as quickly as possible whether the letter that appears is an “x” or an “o.” On 25% of the trials, however, a tone sounds indicating that the response should be interrupted (stop trials). The timing of the warning tone is varied to enable estimation of how much warning the individual needs, interpreted as speed or efficiency of the stop process. Physiological data have demonstrated that response interruption on this task involves both central and peripheral mechanisms.²²⁸ Both lesion data and imaging data indicate that this ability involves a circuit in the brain that includes the right inferior frontal gyrus and the striatum.^{229,230} Brain recording data in primates indicate that specific neurons in these brain regions are active during response interruption.²³¹ The computerized measure has excellent reliability.²³²

Heritability of these individual measures has not been well established, although forthcoming data appear to place heritability of stop-go task stop-signal reaction time (SSRT) at $<.50$, the antisaccade task at about $.56$ (E. Willcutt, personal communication, January 2007), and the go/no-go task at $<.50$.²³³ However, it is notable that when a latent variable is constructed from these response inhibition measures, it appears to have more robust heritability, although this latent variable heritability has varied widely in two studies from $.48$ to $.99$.^{234–236} The promise of this function as an endophenotype appears to rely upon utilizing latent variables (an approach not yet attempted to evaluate risk for smoking

onset or persistence) or the hope that the less-heritable individual measures will be genetically simpler than the phenotypes to which they are indexed. No evidence on this last point has emerged. However, the brain circuitry involved is dopaminergically modulated and also appears to depend on acetylcholine receptors.²²⁷ Thus, examination of receptor genes for dopamine and acetylcholine may clarify the endophenotypic value of these measures.

Further, surprisingly few data are available regarding response suppression and risk for smoking onset. It is unclear whether stop-go task performance predicts smoking initiation or progression to regular smoking and nicotine dependence. One study found that the SSRT was significantly improved following nicotine administered via transdermal nicotine patch in nonsmoking adolescents diagnosed with ADHD.²⁰¹ Another study of healthy adult regular smokers did not find acute effects of nicotine on this inhibition measure.²³⁷ With respect to the go/no-go task, smokers tend to show more impulsivity on these measures than do nonsmokers.²³⁸

P300 Event-Related Potential

Several EEG/ERP measures may be worthwhile as endophenotypes. However, the aspect most studied in relation to smoking risk is the P300 wave. The P300 is an ERP component thought to be related to working memory and stimulus evaluation. As such, it probably indexes cortical activity. It is typically assessed by having an individual complete a computerized attention task or go/no-go task with unexpected events included in a minority of trials (sometimes called “oddball” trials). The individual has to evaluate this event and update working memory; this is thought to be indexed by differences in the peak amplitude (strength) and speed (latency) of the ERP response at 300 milliseconds. Initial data in adults indicate that the reliability of

this index is excellent ($>.80$), and heritability of the amplitude is moderate to high, in the range of .6 to .7;²³⁹⁻²⁴¹ heritability may be higher in males than in females,²⁴¹ whereas heritability of latency was unclear.²³⁹ Hence, the focus here is on the P300 amplitude.

P300 amplitude appears to have important linkages at the phenotypic level with smoking and related risk behaviors. In a community sample of 17-year-old males, reduced P300 amplitude was related to externalizing behavior (defined as the common factor underlying nicotine and other drug dependence, conduct disorder, and adult antisocial behavior).²⁴² A series of studies from the Minnesota Twin Family Study has shown that reduced P300 amplitude at 17 years of age predicted the subsequent development of substance-use disorders, including nicotine dependence.^{241,243}

The P300 may be related to persistence as well as to onset. Studies of adults found lower P300 amplitude in current smokers compared to never smokers, whereas former smokers did not differ significantly from never smokers.²⁴⁴ In addition, the amplitude has been shown to be reduced in nicotine-abstinent adults compared to nonsmokers but, after smoking, was equivalent to that of nonsmokers.²⁴⁵ Further clarification of the state or trait characteristics of this measure in relation to onset and persistence appears to be warranted.

Other Candidate Tasks

A wide range of other psychometrically reliable measures relevant to cognitive control are available and may warrant exploration. Their heritability data, however, varies. Key examples are as follows. First, measures of working memory tap cognitive control systems and are strongly related to risk for psychopathology.^{42,246} These include such measures as counting and sentence span (the child recalls and repeats ever larger lengths of items, sometimes

backwards or while doing a competing task), and N-back tasks (the child updates working memory with a new total every N-items, e.g., every three items). These tasks have excellent validity with regard to neural activation in dorsolateral prefrontal cortex,²⁴⁷ psychometric reliability, and theoretical coherence. Their individual heritability appears to be modest, in the range of .4.^{233-235,248} However, they may be influenced by a simpler genetic architecture involving the noradrenergic alpha-2A receptor gene²⁴⁹ and dopaminergic genes. These measures, however, have not been widely studied with regard to their phenotypic or genotypic association with smoking onset.

Second, measures of set shifting or task switching have become quite sophisticated in their ability to assess cognitive control.²⁵⁰ Simple neuropsychological measures such as the card sorting tasks, in which the individual must remember the working rule for sorting cards (e.g., by color, number, or shape) while problem solving errors, are of interest. These tasks have large validation literatures indicating that they entail activation of the dorsolateral prefrontal cortex.⁶³ Although heritabilities based on single measures are modest (in the range of .50),^{234,251} a composite latent variable of set shifting on card sort measures has heritability approaching .80.²³⁴

Third, direct neuroimaging measures of brain morphometry have been utilized very little in assessing smoking risk. However, because brain imaging measures show moderate associations with other risk phenotypes (such as ADHD), they may be worth pursuing. Further, substantial data show that a range of relevant morphometric measures have heritability exceeding .8^{252,253} or are highly familial,²⁵⁴ and that some directly relevant functional activation patterns are also quite heritable, including relevant activation in the anterior cingulate cortex during stimulus appraisal.²⁵⁵

For PNS concomitants of regulatory control, more consideration is warranted of the utility of parasympathetic response measures. For example, an extensive physiological literature suggests that heart-rate variability, and cardiac vagal tone in particular, is a potential index of regulatory processes.^{256–259} The parasympathetically mediated cardiac response reflected in vagal tone is operationalized as respiratory sinus arrhythmia (RSA) both at rest (high resting levels associated with greater response potential) or in response to an attentional challenge (stronger response to challenge associated with better regulation). RSA reactivity in this situation is viewed as a direct index of effortful control because reactivity of heart rate is directly suppressed by neocortical action during attention,⁴⁵ which, in turn, inhibits sympathetic influences to keep heart rate low (although findings vary somewhat with age). If weak regulatory control is associated with smoking risk, adolescents who go on to smoke would be expected to have weaker RSA response to attentional challenge compared with other adolescents.

Finally, important to note, though more elusive, is the concept of “executive functioning.” Its usage here refers to response suppression and working memory as elements of cognitive control; in this case, *executive function* means the complex, temporal organization of multiple steps (such as completing a recipe). It requires planning, which is assessed on tasks such as the Tower of London that require multistep operations. Planning involves working memory, but also reasoning and intelligence, as well as suppression of competing responses; thus, it is multicomponential. Although these types of planning tasks have been notoriously poor in reliability, some versions have become more reliable.²⁶⁰ However, they are for the most part unstudied with regard to heritability.

Attention and Alertness

Two related ideas are introduced here: attention and alertness. Attention is how people select information, from the nearly infinite amount of input available, for further processing. It is influenced in turn by two types of mechanisms. One type of mechanism is bottom-up and relatively automatic (for example, capture of attention by a sudden movement or sound, or involuntary attraction of attention to a frightening possibility). A second type of mechanism is top-down, effortful, and goal directed (for example, ignoring others talking to finish an important memo for a deadline). It may be that bottom-up, motivated processes cause attention to be easily captured by the possibility of nicotine (or other drugs) or make one susceptible to societal images or opportunities to use cigarettes. For example, attraction to novelty, wish to escape from anxiety, or other motives may “bias” attention toward drug-related information in the environment, and thus, influence initial substance experimentation. Important neural systems are the posterior-anterior cortical loops as well as neural loops from the limbic system to the prefrontal cortex.

Alertness (related to the older concept of arousal) modulates cognitive control. Alertness reaches its nadir in sleep and its zenith during episodes of panic. In day-to-day adaptation, alertness enables one to notice and mobilize a response to important information (bringing the system into readiness) and to maintain attention on an important issue (maintaining readiness).

For alertness or arousal, relevant neural structures include a right-lateralized network of neural structures that include the noradrenergic system originating in the locus coeruleus, the cholinergic system of the basal forebrain, the intralaminar thalamic nuclei, the right prefrontal cortex,²⁶¹ and possibly the ascending

reticular activating system (the latter is related to wakefulness). Probes of this system include simple reaction time on fast-react tasks, response variability, response time to unwarned left-visual field targets, EEG slow-wave activity, excess vigilance decrement, and signal detection efficiency.²⁰⁹ A continuous performance task (CPT) is one in which the individual must identify a rare target in a field of events (similar to a radar operator watching for an occasional missile amid many birds and friendly planes). One hypothesis, for example, would be that excess resting slow-wave activity on an EEG is a liability marker for increased risk of smoking. As shown in table 8.1, EEG theta rhythm (slow-wave activity) is the most advanced of these measures with regard to reliability and heritability data and the most recommended endophenotype for liability studies from this group. Early ERP components, such as the N1 and the P2, also may have promise here, although initial data indicate they are less reliable and heritable than the slow-wave indices. See chapter 9 for a discussion of research linking the EEG and the ERP, as well as CPT responses, to persistence of smoking. Relatedly, multiple measures of attentional control are available. Gardner and colleagues¹⁵³ used a cue-orienting task and found that attentional control was correlated with nicotine use.

Note that cholinergic (nicotinic) receptors are important in attentional function and modulation of dopaminergic activity. These receptors may be involved in smoking onset as preexisting vulnerabilities that contribute to attraction to nicotine via low arousal, energy, or attention. However, given a dearth of data on that point and the obvious relevance of cholinergic systems to response to initial exposure, those endophenotypes are discussed later in this chapter.

Affiliation and Hostility

As a final note, many personality models include an affiliation dimension.^{42,49,51,66,262}

This trait may be relevant in view of the data cited earlier on hostility and smoking onset. However, aside from direct trait measures of hostility, consideration of this trait does not introduce additional low-level experimental paradigms at the present time and is not considered in further detail here.

Smoking and Nicotine-Dependence Risk: Summary and Future Directions

Table 8.1 lists the major measures discussed and what is known about their relevant characteristics. The higher-order traits can be conceived as part of a hierarchical model rooted at the most abstract level in reactivity of basic approach and withdrawal neural systems in early life but that differentiates into additional meaningful lower-order behavioral response systems during childhood. Differentiated at a four-factor level, which is useful for a broad overview, these include (1) an *approach* system related to responses to potential reward; (2) a frontal-limbic *avoidance* system related to stress-response systems and sympathetic autonomic response; (3) a *control* system that is multicomponential and related to cognitive operations such as working memory and response inhibition; and (4) a closely related *affiliation/empathy* system, related to effortful control and also to the capacity for negative affect, leading to empathy and a desire for and tendency toward affiliation and cooperation (as opposed to social dominance or social interaction, which are reflected in the reward-based socializing influenced by reward/approach systems). The affiliation/empathy system may not emerge distinctly throughout childhood, but it may be notable in adolescence. It may be better thought of as personality than as temperament. However, further examination of this system (or trait) in younger children remains of interest. (For more discussion

of distinctions and similarities between temperament and personality, see Nigg.⁴²⁾

The higher-order trait domains all have some promise in relation to smoking risk. It may be that there are multiple routes to risk or that smoking risk is overdetermined biologically. However, these traits are best understood in relation to lower level neural systems, which, in turn, points to more molecular cognitive or physiological measures that can be examined as endophenotypes. The traits themselves will continue to be subjected to genetic investigation, but they are unlikely to be genetically simpler than smoking itself.

As outlined here, a range of context-sensitive physiological measures are candidates to tap these systems at a lower level of analysis than personality. However, as table 8.1 demonstrates, data on basic properties, such as heritability, familiarity, performance in unaffected relatives, or even reliability, remain limited for many of these candidate measures. Such basic work will be needed before their promise can be fully evaluated. On the other hand, some measures already have promising preliminary characteristics and may warrant more aggressive examination in relation to smoking risk.

Initial Nicotine Exposure Response: Conceptual Framework and Candidate Endophenotypes

This chapter addresses a general approach to the study of factors that increase vulnerability to nicotine dependence in adolescents in an effort to identify endophenotypes that may index this vulnerability. As discussed up to this point, most of these factors are likely to be present and, for the most part, measurable before

the onset of tobacco exposure. However, some factors predisposing to dependence in youth may be observable only in response to initial tobacco (or nicotine) exposure. Obviously, escalation to dependence is not possible in those who avoid ever being exposed to tobacco in the first place, even if they otherwise are at great vulnerability for dependence. Among those ever exposed, escalation to dependence is actually less common than no escalation,²⁶³ suggesting great variability in the consequences of initial nicotine exposure. Factors accounting for variability in the short-term consequences of initial nicotine exposure warrant examination as potential predictors of nicotine dependence. There appear to be unique as well as common behavioral and genetic factors that predict the risk of smoking initiation, response to initial nicotine exposure, and subsequent smoking progression.^{21,23,264,265} This section focuses specifically on the effects of initial exposure to nicotine that may lead to progression in smoking behavior and nicotine dependence. It departs somewhat from a model of neural networks and moves to a model at a lower level of analysis involving synaptic reactivity to nicotine. This model is more appropriate to what is known about the physiology of nicotine response. Ideally, future research will examine initial responsiveness to nicotine within the comprehensive framework presented in the first section of this chapter to build a more complete picture of vulnerability to nicotine-dependence risk in children that includes both general and specific streams of risk influence at the genetic level.

This discussion, therefore, begins by considering the sensitivity model. This is a theoretical model of vulnerability to dependence that provides the starting point for considering endophenotypes of initial nicotine exposure. An alternative, the exposure model, is also noted. In brief, these models predict that greater or lesser initial sensitivity, respectively, to drug

effects increases vulnerability to onset of dependence. Because sensitivity to the same responses is relevant to either model, the same literature can be used to evaluate both models. However, as detailed below, the sensitivity model may have greater support and is used as the framework for identifying potential initial nicotine exposure endophenotypes. Nevertheless, variability in initial sensitivity to nicotine effects—either greater or lesser—may in fact have no consistent association with subsequent risk of dependence. This research is being examined in this chapter because of substantial plausibility for the role of sensitivity in dependence risk, despite a lack of clear empirical support that greater initial sensitivity prospectively predicts risk. The evidence for a potential endophenotype is considered within the methodological constraints of the existing literature. This section closes with a discussion of the research needed to fill the gaps in knowledge about initial nicotine exposure and promising endophenotypes.

Theoretical Support for “Innate” Sensitivity to Nicotine as an Index to Dependence Vulnerability

Vulnerability to dependence may be associated with the magnitude of an individual’s initial sensitivity—upon first exposure—to the rewarding and reinforcing effects of smoking, and specifically, nicotine. Evaluating this potential mechanism of vulnerability requires assessment of acute responses to early exposures to smoking (or other methods of administering nicotine). For many reasons, including substantial practical and ethical issues, little research in humans has prospectively examined whether sensitivity to initial nicotine exposure is associated with greater risk of dependence. Yet, this notion has some theoretical support and is bolstered by animal research findings.

Theoretical support for this notion comes from the sensitivity model of dependence vulnerability.²⁶⁶ This model essentially states that individuals who have higher “innate” sensitivity to nicotine will experience greater positive (i.e., pleasurable), but perhaps also aversive, effects from initial experience with nicotine. Such individuals will quickly become tolerant to the aversive effects, allowing the relative enhancement of positive effects. These changes result in greater reinforcement from smoking, promoting escalation of use and the onset of dependence. Those with lower innate sensitivity will be less likely to continue experimenting with tobacco because of a lack of positive effects. “Innate” sensitivity is sensitivity to nicotine upon first exposure and is based on genetic and other constitutional factors. It can be assessed only during “early” experiences with nicotine. It cannot be directly measured after the escalation of smoking frequency beyond experimentation (e.g., daily smoking) because of the onset of chronic tolerance, which is reduced sensitivity to nicotine as a function of tobacco exposure history.²⁶⁷ Onset of chronic tolerance and other indices of adaptation to chronic nicotine may be rapid,²⁶⁸ leaving only a narrow window of tobacco exposure occurrences during which to assess “innate” sensitivity to nicotine. These methodological issues will be discussed further below.

The sensitivity model is derived largely from animal research,^{269,270} which shows that some rat strains are more sensitive than others to nicotine upon initial exposure, and these strains may show greater acquisition of nicotine reinforcement. Thus, greater initial sensitivity may directly promote processes of nicotine dependence in humans, especially adolescents, and individuals who are more sensitive to nicotine upon initial exposure may be at greater risk of smoking progression and subsequent nicotine dependence compared to those who are less sensitive to this initial exposure.

The Exposure Model: An Alternative View of Initial Response to Nicotine

In contrast to the sensitivity model of initial nicotine exposure, the exposure model proposes that reduced, not enhanced, initial sensitivity predicts greater risk of nicotine dependence. The rationale for this idea is that experiencing few *aversive* effects from smoking makes subsequent experimentation more likely, such that other effects of nicotine can begin to produce changes that lead to dependence. Also, such individuals from the very outset may take in larger drug amounts to counter their attenuated sensitivity. This greater consumption can accelerate the consequences of heavy drug exposure, including dependence and physiological pathology. The exposure model is derived mostly from the alcohol research literature, especially studies of alcohol responses in offspring of alcoholics compared to controls.^{a,b} Disparities between the sensitivity and exposure models may stem from the different substances involved, which may induce dependence either by unique and different processes, or by the different responses assessed.^{a,c} Supporting the latter possibility were findings from a study of women either with or without a paternal history of alcoholism who were given an acute dose of alcohol.^d Those with a positive paternal history exhibited less impairment due to alcohol on one performance task—digit-symbol substitution—consistent with the exposure model. Yet, they showed greater reward responses to alcohol (e.g., “liking,” “good drug effect”), consistent with the sensitivity model, as well as more impairment on a second performance task—digit recall. Other research also has found greater, rather than lesser, sensitivity to the intoxicating effects of alcohol (as well as barbiturates) in men with a positive family history of alcoholism.^e Thus, because the sensitivity model has somewhat more support in explaining the association of some responses to nicotine-dependence risk, potential endophenotypes are evaluated from the perspective of the sensitivity model.

^aEng, M. Y., M. A. Schuckit, and T. L. Smith. 2005. The level of response to alcohol in daughters of alcoholics and controls. *Drug and Alcohol Dependence* 79 (1): 83–93.

^bSchuckit, M. A., and T. L. Smith. 1996. An 8-year follow-up of 450 sons of alcoholic and control subjects. *Archives of General Psychiatry* 53 (3): 202–10.

^cPomerleau, C. S., O. F. Pomerleau, S. M. Snedecor, S. Gaulrapp, and S. L. Kardia. 2004. Heterogeneity in phenotypes based on smoking status in the Great Lakes Smoker Sibling Registry. *Addictive Behaviors* 29 (9): 1851–55.

^dEvans, S. M., and F. R. Levin. 2003. Response to alcohol in females with a paternal history of alcoholism. *Psychopharmacology (Berl)* 169 (1): 10–20.

^eMcCaul, M. E., J. S. Turkan, D. S. Svikis, and G. E. Bigelow. 1991. Alcohol and secobarbital effects as a function of familial alcoholism: Extended intoxication and increased withdrawal effects. *Alcoholism, Clinical and Experimental Research* 15 (1): 94–101.

Overview of Measures of Innate Sensitivity to Acute Effects of Nicotine

Selected animal studies and the limited human research exploring the notion that variation in innate, or “initial,” sensitivity to smoking or nicotine is associated with risk of nicotine dependence will be examined in this subsection. Endophenotypes that may tap initial sensitivity to nicotine will

be considered, with substantial attention paid to the practical problems in conducting such research. Owing to a lack of research, one aspect of this model of variability in initial nicotine sensitivity will not be examined, specifically that these individuals rapidly become tolerant to nicotine’s aversive effects, although the potential utility of studying this phenomenon will be discussed in the section “Discussion of Future Directions.” Also, unlike chapter 9, nonpharmacological effects of smoking,

such as conditioned responses to smoking cues (e.g., cue-induced craving), are not included here. The emergence of such conditioning requires extensive exposure to smoking, and the concern here is only with short-term or relatively immediate responses to “initial” (or early) exposure. Similarly, consequences of abstinence from smoking, notably onset of withdrawal symptoms, are not relevant here because these also arise only after extended exposure, as discussed elsewhere (chapters 3 and 9).

Measures of innate sensitivity to nicotine are subdivided here into two areas: (1) initial nicotine reinforcement and reward and (2) initial sensitivity to other effects of nicotine, mostly affective, behavioral, and cognitive performance measures that may help explain initial reinforcement and reward from nicotine use. Reinforcement is a central facet of the dependence process; the persistence of reinforcement from smoking is the hallmark of dependence once it is established. Reinforcement is necessary for smoking’s motivational effects to develop in a regular smoker and, thus, is proximal to processes of dependence. “Reward” is meant here to refer to the hedonic value (e.g., “liking”) of the drug as reported by the user and may reflect subjective responses to drug use that encourage the onset of drug reinforcement. Yet, *why* nicotine acquires motivational effects of being reinforcing and rewarding may also be important and may vary between individuals, perhaps because of genetic or constitutional factors. Other nicotine responses may help explain its reinforcing and rewarding influences and are therefore viewed as more distal to dependence processes. These responses include affective (mood) and physiological effects; behavioral effects related to attention (inattention, disinhibition), which may, in turn, help to regulate mood; and cognitive processing performance (e.g., alertness), which may have indirect effects on a sense of well-being. Note that this same organizational framework, involving two

broad areas of motivational effects and other smoking effects, is used in chapter 9 to evaluate potential endophenotypes of dependence in chronic smokers.

For the measures of nicotine reinforcement, reward, and mood effects, the information is sufficient to address, if not draw conclusions on, some or all of the criteria of a putative endophenotype for nicotine dependence (e.g., biological plausibility, predictive validity, heritability or a sufficiently broad distribution of responses to the measure in the population, and reliable measurement). These criteria are relevant to the utility of these measures in research on the genetic determinants of nicotine-dependence risk, and all need to be demonstrated to verify that the measure is a likely endophenotype. For example, some measures may have a strong rationale for relevance to dependence, and some evidence linking them to dependence, but no evidence on heritability or reliability. For others, heritability and reliability may be strong, but their link to dependence risk may be unknown. In either case, the missing information seriously limits the utility of the measure in genetic research on vulnerability to nicotine dependence. A subsequent discussion will point out the additional research needed to fill in these gaps and fully evaluate these measures as endophenotypes for vulnerability to nicotine dependence.

General Methodological Concerns with Innate Sensitivity Research

Several concerns that limit the interpretation of results of research in this area need to be kept in mind. First, what constitutes “initial” exposure is not necessarily clear. Ideally, “initial” should be only that exposure to tobacco occurring before the onset of chronic changes in sensitivity to nicotine due to extended

tobacco use. The most common changes are chronic tolerance, or reduction in sensitivity, and the onset of withdrawal in the absence of nicotine, which also can influence responses to nicotine, as discussed to a greater extent in chapter 9. How much exposure is needed to precipitate these changes is not known, but it may be very modest.^{268,271} It is probably fewer than 100 cigarettes, which is the standard cutoff of exposure that differentiates never smokers from ever smokers in epidemiological research.²⁷² How many fewer is uncertain. Much of the research on adolescents does not specify the amount of tobacco exposure that individuals have had. However, some research on initial sensitivity in young adults has limited such exposure to fewer than about a dozen lifetime uses of tobacco products.²⁷³

Second, the most rigorous method of assessing initial sensitivity is prospectively, such as by administering nicotine to naive subjects, ideally young adolescents, to simulate “initial exposure.” This is problematic, however, for obvious ethical reasons, so most of the research on adolescent responses to smoking is retrospective self-report. In some studies, the self-report of adolescent responses is assessed when these individuals have become adults, years after the initial smoking exposure, increasing the potential for poor or biased recall. Asking adolescents who recently initiated smoking to recall their responses to initial smoking just one year later does not appear to reduce the problem of decay in recall accuracy.²⁷⁴ Adolescents are also inconsistent in recall of a fact that should be much easier to remember, the age at which they initiated smoking,²⁷⁵ causing further concern about the reliability of retrospective data on smoking. Similarly, participants may recall responses to a particularly salient adolescent smoking experience but not “initial” exposure. A later study examining prospective nicotine effects as a function of

retrospective self-report of early smoking experiences in young adult nonsmokers suggests some validity for self-report of two similar effects—dizzy and buzzed—but less so for other effects.²⁷⁶

Third, differences in sensitivity to initial smoking exposure cannot be easily interpreted without control over the amount of nicotine exposure, or “dose.” However, the “dose” of this exposure is not controlled: some adolescents will self-administer significant amounts of nicotine from initial smoking, and others may not inhale sufficiently to obtain much nicotine upon first exposure. Variation in responses to nicotine due to *variation in self-dosing* has far different biological implications than does variation in responses to the same nicotine dose due to *variation in tissue sensitivity* to nicotine. Retrospective reports cannot distinguish between these potential causes of variability in apparent sensitivity. A similar concern is lack of control over the context of initial smoking exposure. Responses, and thus sensitivity, may vary as a function of situational factors (e.g., other drug use, social factors, mood), which are uncontrolled in initial smoking exposure of adolescents.

Fourth, a strategy used to get around the problems inherent in retrospective self-report could be to administer nicotine via novel methods (i.e., other than smoking, such as by nicotine gum, patch, or spray) to young adults with little or no prior tobacco exposure. This approach allows for controlled exposure to nicotine in young individuals who have not become tolerant, and would truly reflect initial sensitivity, without the abuse liability of smoking. One concern with this approach is whether responses to novel nicotine generalize to responses to initial tobacco smoking. A second concern is whether differences among individuals in nicotine sensitivity “track,” or persist unaltered, from youth to adulthood. If not, genetic

factors responsible for variability in initial sensitivity among adults may not relate to sensitivity among youth.

Finally, assessing initial sensitivity requires participants who are willing to be exposed to nicotine through self-selected experimentation with tobacco or self-selected exposure through research. It is not clear if results would generalize to individuals who choose to avoid any exposure to nicotine, even for research purposes. Thus, individual variability in sensitivity to nicotine responses may not generalize to all naive individuals at risk. (Note that “initial” exposure is not considered here to include in utero exposure to smoking or nicotine, and this influence on risk of nicotine dependence will not be examined.²⁷⁷)

Initial Sensitivity to Smoking or Nicotine: Reinforcement

Reinforcement

A drug is reinforcing if it is self-administered more than an inert comparison substance (e.g., placebo). Drug reinforcement is the sine qua non of dependence in that dependence on a substance cannot occur if the substance is not reinforcing. Thus, the magnitude of the reinforcing effects of nicotine upon initial exposure likely contributes to a greater probability and faster speed of becoming dependent. As discussed in more detail in chapter 9, reinforcement is believed to comprise several related concepts (e.g., drug seeking or drug-motivated behavior, drug preference, inability to abstain from drug use or persistence of use) that are assessed with different procedures. The amount and persistence of smoking self-administration are critical indices of nicotine dependence among those who have become established smokers, after chronic exposure to smoking. With initial exposure to nicotine, however,

these measures are not as applicable because intake is very limited in frequency, by definition. Most of these procedures are not included here because they are less relevant during initial exposure. (Similarly, the influence of nicotine on enhancing reinforcement from other reinforcers may not be very apparent with initial exposure to the drug and is also not discussed here, although it is addressed in chapter 9.) Possible measures of initial reinforcement outside the laboratory are shorter intervals between smoking exposures and the amount of cigarette consumption (e.g., nicotine or smoke intake) per exposure. However, objective measurement of these variables is difficult, necessitating self-report. An alternative laboratory-based procedure, nicotine choice, may be able to objectively index initial reinforcement from nicotine per se and will receive the most specific attention because of its promise as an endophenotype. Other potential endophenotype measures will also be noted.

Biological Plausibility of Reinforcement Measures

A number of species acquire robust nicotine self-administration that persists in the face of increased response requirements, and abstinence from nicotine in such animals leads to a syndrome of withdrawal signs.²⁷⁸ Although nicotine self-administration in nonhuman animals may not be completely homologous with tobacco, or even nicotine, self-administration in humans, the similarity of factors that influence this behavior in both groups is notable.²⁷⁸ In regard to initial sensitivity to nicotine reinforcement, Donny and colleagues²⁷⁹ found in rodents that more rapid acquisition of nicotine self-administration across days predicted a greater subsequent intensity of nicotine-motivated behavior (higher breakpoint on the progressive ratio test), a component of reinforcement related to dependence. The difference in self-administration was very small at the start of acquisition

(i.e., “initial exposure”) but grew over time. In examining neurobiological differences between the animals who rapidly, as compared to slowly, acquired nicotine self-administration, Donny and colleagues²⁷⁹ found that the former tended to be those with less density of nicotine receptors in the brain by the end of acquisition. Thus, certainly in animals and probably in humans,¹⁶¹ onset of nicotine reinforcement can occur very early after first exposure, and the subsequent escalation of use varies significantly. However, the findings by Donny and colleagues²⁷⁹ question whether the former directly causes the latter; that is, that differences upon initial exposure are robustly predictive of the rate of onset of dependence.

Other factors associated with the acquisition of nicotine self-administration in animals are also being examined. Differences in nicotine reinforcement between rodent strains are discussed extensively in chapter 9. In addition, rats bred for high alcohol consumption tend to show greater acquisition and persistence of nicotine self-administration, suggesting overlap in the factors producing vulnerability to alcohol and nicotine dependence.²⁸⁰ Greater locomotor response to novelty has been studied as an indicator of greater predisposition to self-administer stimulant drugs,²⁸¹ several studies have found an association between this response and greater acquisition of nicotine self-administration in rats²⁸² as well as in mice.²⁸³

Nicotine Choice

Description and Rationale of Measure.

The amount of smoking frequency upon initial exposure has high face validity as a measure of reinforcement in that the measure involves tobacco smoking behavior. However, this measure does not differentiate whether the frequency is due to the effects of nicotine per se or to effects of nonnicotine aspects of smoking. Although conditioned responses to smoking are essentially absent at initial exposure, as noted, various other

nonnicotine aspects of smoking can promote acute smoking frequency, such as social facilitation (e.g., peer approval). Dependence is driven mostly by the effects of nicotine, and genetic influences on smoking are believed to act primarily through these effects. Consequently, when it comes to endophenotypes of initial sensitivity, the reinforcing effects of nicotine per se may be more relevant than the reinforcing effects of tobacco smoking in general, although kinetics of the method of nicotine administration (particularly speed of uptake) could be critical.²⁸⁴

One objective measure of initial sensitivity to the reinforcing effects of nicotine in prospective laboratory-based research is a *choice* procedure, involving choice between substances containing either active nicotine or a placebo.^{285,286} Subjects are instructed to select a specific number of total “uses” (e.g., puffs or, with naive individuals, units of a novel nicotine-delivery method such as nasal spray or piece of gum) from between the two available substances. The greater the choice of active drug versus placebo, presumably the more the drug is reinforcing. A discussion of the pros and cons of this procedure can be found in Perkins.²⁸⁷ Thus, the choice procedure indexes the relative reinforcing effects of nicotine and not necessarily the absolute reinforcing effects. (The latter is shown only when nicotine is chosen more often than placebo, which is not common in nicotine-naive subjects.) So, if nicotine choice is greater in some subjects or under some conditions rather than others, the relative reinforcing effects of nicotine are greater in those subjects or conditions. Variations in the choice procedure, including those more appropriate for use in chronic smokers, are described in chapter 9.

Association with Nicotine Dependence.

Most research on nicotine choice has focused on smokers rather than nonsmokers, but observations of smokers suggest a link

between choice behavior and dependence. For example, among smokers, acute nicotine choice behavior in the laboratory is correlated with self-reported cigarettes per day²⁸⁵ and with difficulty quitting smoking,²⁸⁸ suggesting that choice has concurrent validity in indexing several aspects of tobacco dependence (chapter 9). Studies of initial sensitivity to nicotine reinforcement in young adult nonsmokers indicate that nicotine choice is not greater than placebo choice, whether administered by nasal spray²⁸⁵ or gum.²⁸⁹ However, of greater interest here is the fact that nonsmokers differ very widely in the degree to which they choose nicotine, and a minority of nonsmokers do choose nicotine more than a placebo. Greater choice of nicotine in nonsmokers (and, to a lesser extent, in smokers and former smokers) is associated with greater pleasurable responses (pleasant effects, vigor, arousal) and attenuated aversive responses (e.g., tension, fatigue, confusion) to nicotine.²⁸⁵ On the other hand, several individual-difference characteristics, including personality measures of impulsivity (response disinhibition, delay discounting), are not related to nicotine choice (via nasal spray) in nonsmokers, while other measures (novelty seeking, extraversion) may be inversely related to choice, particularly in women.²⁹⁰ These findings, which contrast with the discussion of predisposing factors in the first section of the chapter, may be specific to nicotine choice via nasal spray and require replication with tobacco smoking, if practical and ethical to do with naive subjects. However, associations of sensation seeking and other impulsivity measures with nicotine “reward” and with certain subjective mood responses to nicotine have been observed, as discussed below. In sum, while nicotine choice has been investigated in nonsmokers, and can provide an objective index of sensitivity to initial reinforcement, no research has prospectively determined that greater nicotine choice predicts greater vulnerability to dependence.

Heritability; Distribution of Responses in the Population. The full range of possible nicotine choice responses has been observed, from zero to 100%, in nonsmokers, when nasal spray is the delivery method. Dose is a key influence on this distribution, as choice of nicotine in nonsmokers is greater with lower doses, which produce less toxicity in naive individuals. When choice is between sprays delivering the equivalent of nicotine from about one-half puff on a cigarette, nicotine is chosen on about 25%–35% of all opportunities, and 15%–25% of adult nonsmokers choose nicotine over one-half the time.²⁹⁰ That even a minority of nonsmokers find nicotine via nasal spray reinforcing in an absolute sense is consistent with the notion of innate predisposition to dependence vulnerability. It is also consistent with other data showing that only a minority, about one-third, of those who ever try tobacco go on to become dependent.²⁶³ This one-third likely includes many of the naive individuals who find nicotine reinforcing at first exposure. Dose may also be critical for identifying individual differences in initial sensitivity to nicotine reinforcement in that nicotine choice is greater in men than in women when higher doses (2.5 micrograms per kilogram [$\mu\text{g}/\text{kg}$]) of nicotine spray are used,²⁹¹ but not when lower doses (1.25 $\mu\text{g}/\text{kg}$) are used.²⁹² Only one study has examined genetic influences on nicotine choice among nonsmokers, finding that those with an absence of the *DRD4**7-repeat allele chose nicotine by nasal spray more than those with presence of the *7-repeat allele; gene variants for *DRD2***TAQIA*, *DRD2***C957T* single nucleotide polymorphism (SNP) *SLC6A3*, serotonin transporter (*SLC6A4*), and mu opioid receptor (*OPRM1*) were not related to nicotine choice.²⁹³

Other Potential Endophenotypes of Initial Reinforcement

Smoking/Nicotine Use Frequency. Little research has examined smoking frequency upon initial exposure, although some

evidence suggests that greater frequency may predict vulnerability to dependence. One prospective follow-up study examined the risk of current smoking in high school as a function of amount of smoking exposure reported when participants were aged 8–10 years. Greater number of cigarettes smoked by that age was linearly associated with greater risk of current daily smoking.²⁹⁴ Yet, this effect may simply be due to younger age of first exposure in that those who smoked more cigarettes by 10 years of age likely smoked their first one earlier than did children who smoked fewer. In terms of potential endophenotypic measures of smoking frequency, a laboratory procedure that may reflect reinforcement as indexed by smoking frequency is simple ad lib use of either nicotine or placebo products in a controlled setting.²⁸⁹ The utility of this ad lib nicotine reinforcement measure as an endophenotype is limited: there are no known data on reliability or heritability in naive individuals, and some research suggests that ad lib use of nicotine via novel means is very limited in such individuals.²⁸⁹

Latency to Subsequent Nicotine Exposure.

Rather than greater frequency of self-administration upon initial exposure being important, it may be that faster escalation of smoking after initial exposure is a more relevant index of nicotine-dependence vulnerability,²⁹⁵ as suggested by the animal work by Donny and colleagues.²⁷⁹ For example, Hirschman and colleagues²⁹⁶ found that latency between the first and second cigarette was an important indicator for adolescents who rapidly progressed to subsequent smoking. In fact, early smoking experiences accounted for significant variance in the model for rapid acceleration, but not for adolescents who progressed slowly to a second cigarette. Other studies indicate that a shorter interval between the first and second cigarette is associated with a greater likelihood of daily smoking.²⁹⁷ Shorter transition times from initiation to regular use are thought to reflect drug reinforcement

and risk for dependence, including tobacco.²⁹⁸ In fact, Audrain-McGovern and colleagues²¹ found that adolescents who had a *CYP2A6* genotype associated with faster nicotine metabolism smoked a greater number of cigarettes and progressed to nicotine dependence at a faster rate (controlling for age of first smoking exposure) compared to adolescents who had a *CYP2A6* genotype associated with slower nicotine metabolism. Development of endophenotype measures of latency between self-administration experiences is challenging because of a variety of practical and ethical concerns. Latency between cigarettes may be very long in experimenting adolescents, so modeling this latency in laboratory procedures would seem impractical.

Age of Onset. As discussed previously, the younger the age of smoking initiation, the greater the probability of eventual nicotine dependence. Age of initial smoking exposure appears to increase subsequent dependence risk even if no further exposure occurs for several years,²⁹⁹ suggesting either an “incubation” effect of that initial exposure or that early exposure is a marker for other factors responsible for vulnerability. Basic animal research demonstrates that rodents are more sensitive to nicotine effects during adolescence than in adulthood, consistent with this notion.³⁰⁰ Thus, the earlier the initial exposure to nicotine, the greater the likely sensitivity to the drug, which may account for the increased risk of dependence. At first glance, this association would not seem to offer directions for developing an endophenotypic measure because it is based solely on the age of self-selection to smoking initiation. It is difficult to see how this could be captured in controlled research involving nicotine administration in a laboratory setting, but it may serve as a marker in prospective research predicting smoking progression and nicotine dependence. However, genetic influences may differ by age,⁴ and eventually, age of onset may be a clue to genetic effects.

To take advantage of this, investigations would have to disentangle the influence of age of onset on greater smoking frequency²⁹⁴ and on faster escalation of smoking.²⁹⁸ Research also would have to control for psychiatric comorbidity that partially may account for early onset.¹⁴³

Initial Sensitivity to Smoking or Nicotine: Reward

Description and Rationale of Reward Measures

Although reinforcement is in many respects the essence of dependence, other acute effects of smoking or nicotine may index processes relevant to the development of dependence and vulnerability to dependence. Drug reward is one such effect. *Reward* does not have as specific a definition as reinforcement but is often viewed as the hedonic value of a substance. In this context, *hedonic* means the subjective evaluation of the substance's incentive-motivating effects (see Everitt and Robbins³⁰¹ for a discussion of the distinctions among subjective responses, reward, and reinforcement). Rewarding effects of drugs are often seen as a primary cause for the initiation and maintenance of drug self-administration (reinforcement), although some theories question their importance after the onset of dependence.³⁰² Reward is different from subjective measures of mood, discussed later, which are commonly obtained in studies of drug effects. Mood measures are (typically) self-report ratings of the subjective mood state of the person. By contrast, reward is a subjective rating of the hedonic characteristics of the substance itself, albeit from the user's perspective, obtained immediately after using the substance. Thus, while mood effects of substance use may influence reward (and reinforcement), they are certainly not the same thing. As with reinforcement, reward can only be measured concomitant with actual substance

use, while the subjective mood state of the user can be assessed at any time, even in the absence of the subject ever using the substance. Typical measures relevant to reward in humans are ratings of "liking," "good effects," or "bad effects" of the substance completed on 7-point Likert or visual analog scales. The extreme-response options for each item may be anchored by "not at all" to "extremely." Little research has documented the reliability of such responses to initial nicotine intake, although research in adult smokers suggests good reliability, as noted in chapter 9.

Biological Plausibility of Reward Measures

Neurobiological changes associated with "liking" and other reward measures in humans have not been extensively studied, and there does not appear to be any such research in naive subjects (i.e., initial exposure). However, research assessing reward via retrospective self-report suggests that greater initial smoking reward is associated with greater risk of dependence. One study of several thousand adults found that 94% of those who reported having liked their early exposures to smoking progressed to smoking at least 100 cigarettes in their lifetime (the standard epidemiological definition of a lifetime smoker) compared to only 57% of those who reported no liking of their early exposures to smoking.³⁰³

Because animals cannot provide self-report ratings, there may be no directly homologous measure of reward in animals. However, two measures that may be used to model reward are the conditioned place preference (CPP) procedure and intracranial self-stimulation (ICSS) procedure. In the CPP procedure, animals are placed in distinctive environmental contexts (e.g., different sides of a partitioned box) after receiving injection of either drug or saline, with each paired to one of the contexts. After several pairings of each,

the animal is then tested for preference for one or the other context by the amount of time it spends in each when allowed to move freely between them. Greater time spent in the drug-paired side is believed to index preference for the drug (versus saline), while less time spent in the drug-paired side is believed to index aversion to the drug. The ICSS measures the intensity of electrical stimulation in the brain required to maintain behavior, similar to drug self-administration paradigms in animals. Drugs or other conditions that increase the intensity of stimulation necessary to maintain behavior appear to be aversive, whereas drugs or conditions that decrease this intensity appear to be pleasurable. Most drugs that produce dependence in humans, including nicotine, decrease the intensity of stimulation required to maintain responding. The CPP and the ICSS are discussed more extensively in chapter 9.

Association of Reward Measures with Nicotine Dependence

Very little research has examined factors associated with greater nicotine or smoking reward in humans upon initial exposure. However, greater pleasurable responses to initial nicotine spray (such as vigor and pleasant effects) were found to predict greater subsequent nicotine choice in nonsmokers.²⁸⁵ Also, smokers report greater “liking” in response to nicotine nasal spray, compared to nonsmokers, showing concurrent validity of reward with dependence.²⁷³ It is unclear if other research exists relating rewarding effects of initial nicotine or smoking exposure to dependence vulnerability.

Heritability; Distribution in the Population

The limited research on initial sensitivity to nicotine reward precludes much information on variability in this response.

However, in a study of individual differences in nicotine sensitivity in 131 young adult (aged 21–39 years) nonsmokers administered nicotine via nasal spray, reward ratings (want more, satisfying) were higher in men, but not in women, as a function of novelty seeking.²⁹³ Genetic variants related to dopamine function were largely unrelated to reward in nonsmokers, although *DRD2*C957T* SNP (*TT* or *CT* versus *CC* genotype) and *DRD4* (presence of *7-repeat allele versus absence) were associated with stronger perception of nicotine effects from the spray.²⁹³ Other analyses showed greater responses on some reward ratings in those with two rather than one or no parents who were smokers and as a function of earlier experience with marijuana.²⁹² Existing levels of caffeine or alcohol use were unrelated to nicotine reward. These findings should be interpreted with caution; they were conducted with young adults who had self-selected to nonsmoking status, and results with a more heterogeneous sample including those at greater risk could show different results.

Initial Sensitivity to Other Responses to Nicotine

Other responses to initial nicotine exposure may also provide information about valid endophenotypes related to dependence risk, especially effects that relate to affective regulation. Other effects that could be relevant but have generally not been studied in naive users will be very briefly noted. These include behavioral effects related to attention and impulsivity as well as cognitive-processing performance after initial nicotine exposure. The same concerns about the limitations of research on initial exposure presented earlier apply to studies of sensitivity to these responses.

Affective/Mood Responses

Most of the research in this area of other responses to nicotine as potential endophenotypes focuses on self-reported

mood (affective) responses to smoking or nicotine. Yet, as discussed in chapter 9, mood is believed to comprise effects measurable across several response domains, including physiological, behavioral, and cognitive. Studies limited to self-report likely fail to adequately characterize mood and the endophenotypes of initial sensitivity to nicotine's mood effects.

Biological Plausibility

Some self-reported mood effects of smoking ("euphoria" and "elation," which may be similar to "head rush or buzzed") in smokers have been related to dopamine release in the striatum.³⁰⁴ Increases in dopamine in the striatum and ventral tegmentum are believed to be critical to nicotine reinforcement.³⁰⁵ This is consistent with effects in the approach system described earlier and would be expected to make rewards more salient and satisfying. This would also enhance attentional focus, leading to a potential cascade of reinforcing effects. It was also noted in the first part of this chapter that mood-related factors may bias attention toward drug-related relief and influence dependence onset. However, these effects may be even more powerful in maintaining smoking after the onset of dependence (chapter 9).

Plausibility also comes from clinical or retrospective reports of mood effects from initial smoking. In several studies, adults who were current smokers retrospectively reported having had greater pleasant sensations and "head rush" or "buzz" the first time they ever smoked compared to adults who were currently nonsmokers but had some smoking exposure.³⁰⁶ Adult smokers also tend to report having had equal or fewer unpleasant responses to their first cigarette, suggesting that greater pleasant effects are important and lesser (or greater) unpleasant effects are not as important. In one study, Pomerleau and colleagues³⁰⁷ reversed the direction of the comparison and examined current smoking

amounts in adults as a function of whether they reported retrospectively that they did or did not experience a "pleasurable rush or buzz" during their first cigarette. Those who said "yes" (i.e., they did experience rush or buzz during their first cigarette as an adolescent) currently smoked more cigarettes per day than those who said "no." Interestingly, those who said "yes" also reported greater "pleasurable buzz" and "euphoric sensations" prospectively in response to acute administration with nicotine nasal spray, suggesting a continued greater sensitivity to one effect of nicotine even after the onset of tolerance due to chronic smoking.

Note that the association between pleasurable responses to early use and subsequent dependence may not be specific to smoking. Greater positive mood responses, but few or no negative responses, to early use of cannabis³⁰⁸ and cocaine³⁰⁹ have been associated with greater indices of dependence to these drugs. Thus, greater mood effects of early drug use may be broadly linked to vulnerability to drug dependence. This research and the studies of smoking responses should be viewed cautiously, given the biases inherent in retrospective recall of drug-use experiences.

Examined next will be research on sensitivity to initial mood effects of smoking assessed by retrospective clinical reports in adolescents varying in amount of current smoking. We will also discuss the few prospective laboratory-based studies of responses to smoking or nicotine in those believed to vary in risk of dependence.

Acute Self-Reported Mood Effects

Description of Self-Reported Mood

Measures. Self-reported mood is assessed with a number of validated measures. Common mood measures assessed in acute smoking or nicotine studies include the Positive and Negative Affect Schedule,³¹⁰ the Mood Form of Diener

and Emmons,³¹¹ and the Profile of Mood States.³¹² The measures and results from studies of acute mood effects of nicotine or smoking administration are presented in Kalman.³¹³ The reliability of these responses to nicotine is very high in both smokers and nonsmokers via nasal spray³¹⁴ and probably via other controlled methods of administration. Assessment of acute mood effects of smoking and nicotine in the laboratory, including the use of measures other than self-report, is discussed more extensively in chapter 9.

As noted above in outlining plausibility, some studies have related self-reported mood effects of initial smoking to risk of dependence by studying adult smokers recalling their experience upon smoking their first cigarette. Most of these studies were done by Pomerleau and colleagues with their self-report measure, the Early Smoking Experiences (ESE) scale.³¹⁵ The responses to smoking include nicotine-related effects of “pleasant sensations,” “unpleasant sensations,” “nausea,” “relaxation,” “dizziness,” and “pleasurable rush or buzz,” and two effects specific to smoke inhalation, “coughing,” and “difficulty inhaling.” Each is rated on a 4-point Likert scale from “none” to “intense,” with a fifth option of “don’t remember.” Unfortunately, test-retest reliability of recall of initial smoking experiences assessed in adolescents a year apart is quite low,²⁷⁴ despite the relative recency of those experiences. Research in adults suggests that the reliability of responses two years apart may be satisfactory if response options are dichotomized (i.e., yes/no, rather than a 4-point scale³¹⁶). However, the ESE may have limited validity, as just two (dizziness, pleasurable rush or buzz) of the six items retrospectively assessing pharmacological effects of smoking predicted prospectively assessed nicotine nasal spray effects on those same items in young adult nonsmokers,²⁷⁶ although comparing nicotine administration via the same method would provide a stronger test of validity.

Association with Dependence Risk. There appears to be no prospective research relating acute mood responses to nicotine in nonsmokers to indices of dependence risk. However, a number of studies of recall of recent smoking experiences in adolescents or young adults demonstrate some association between sensitivity to these mood effects and dependence. The potential advantage here over the retrospective studies in adults noted previously is that the recall of experience with initial smoking may be more reliable since less time has passed. In two studies of adolescents, recall of being “relaxed” in response to their first cigarette was strongly associated with subsequent onset of dependence, as defined by smoking at least monthly¹⁶¹ or weekly.²⁷⁴

In perhaps the most rigorous study of this kind in smoking, Hu and colleagues³¹⁷ reinterviewed 15,000 young adults (mean age of 22 years) who had been included in earlier national surveys of adolescent health. Retrospective reports of greater pleasant effects and dizziness (related to “head rush”) but lesser unpleasant effects from initial smoking increased the risk of progressing to daily smoking in those who had ever been exposed. Pleasant effects, but not dizziness or other unpleasant effects, were also associated with greater risk of transition to dependence among those who ever smoked daily. However, persistence of smoking (i.e., failure to quit) among those who were ever dependent was weakly related to lesser, not greater, pleasant and unpleasant effects from initial smoking. Thus, greater initial sensitivity to pleasant effects of smoking may influence the early progression to daily smoking and onset of dependence but is less important in explaining persistence of smoking once dependence is established. This observation perhaps further exemplifies the difference in factors promoting onset versus persistence of dependence, as represented in this chapter and chapter 9, respectively.

Several older cross-sectional studies compared reports from early smoking in adolescents with minimal lifetime exposure (just a few cigarettes) compared to those with greater exposure. Those adolescents who were currently smoking to a greater degree reported having experienced greater pleasurable effects (e.g., “feeling high”) and fewer aversive effects (e.g., “feeling sick”) at their initial exposure to smoking than did adolescents with little current smoking (see review in Eissenberg and Balster).³¹⁸ Similarly, among adolescents who smoked, reports of greater “relaxed,” “high,” and “dizziness” (similar to “rush or buzz”) and lower “cough” from first cigarette were associated with faster escalation of smoking, while other aversive effects had no association.^{296,319} Interestingly, similar findings were reported in a study of Chinese 10th graders, demonstrating cross-cultural consistency in the relationship between pleasurable responses to initial smoking and subsequent smoking escalation.³²⁰

One study tested whether pleasant or unpleasant initial smoking experience mediated the relationship between the *CYP2A6* genotype (genetic variation in nicotine metabolic inactivation) and nicotine dependence. *CYP2A6* did not have a significant effect on either pleasant or unpleasant initial smoking experience, negating the possibility of mediation.²¹ These initial smoking experiences may not account for the relationship between *CYP2A6* genetic variation and emergence of nicotine dependence, or the mediated relationship is more complex than modeled. Likewise, adolescents might not view the initial experience as positive or negative, and/or the initial experience may be modified by the presence of other smokers and other substances, such as alcohol or marijuana.³²¹ Consistent with these findings, O’Loughlin and colleagues²² did not find that initial smoking experiences mediated the effect between *CYP2A6* and the odds of becoming nicotine dependent. The role of initial

positive and negative smoking experiences in subsequent smoking warrants further attention. Methodological issues surrounding prospectively measuring initial reactions to nicotine and a lack of attention to the impact of contextual factors may be disguising important relationships. In addition, heterogeneity in the initial responses to nicotine may be hidden by evaluating the average response of the sample rather than accounting for interindividual variation. Some responses (e.g., “head rush,” “buzz”) may be more discriminatory than others (e.g., “dizziness”).³²²

Finally, some research has examined concurrent association between mood responses to nicotine and self-administration by using young adult nonsmokers to simulate adolescents experimenting with smoking. This approach ensures that responses to nicotine in subjects are “initial.” Nicotine is administered via novel means, such as nasal spray, patch, or gum. Using this approach, associations were found between pleasurable mood responses to nicotine via nasal spray and subsequent choice of nicotine in nonsmokers as well as in smokers,²⁸⁵ suggesting that these mood responses are related to nicotine’s reinforcing effects and, perhaps, risk of dependence.

Heritability; Population Distribution of Acute Self-Report Mood Response to Initial Smoking

A prospective study of young adult nonsmokers found greater aversive mood responses to nicotine via nasal spray, such as decreases in vigor and positive affect (but greater buzz) among those with the *DRD4**7-repeat allele compared to those without the *7-repeat allele.²⁹³ Other genes (*DRD2***TAQIA*, *DRD2***C957T*, serotonin transporter, dopamine transporter, *OPRM1*) were not clearly related to acute mood responses to nicotine. The neuronal nicotinic acetylcholine receptors

CHRNA2,³²³ *CHRNA3*³²⁴ and *CHRNA5*³⁴ have been related to several retrospective ratings of initial smoking responses in young adults (dizziness, buzz or rush, relaxed). Regarding impulsivity factors, aspects of the sensation-seeking personality, which is associated with risk of nicotine and other drug dependence (see earlier sections of this chapter), have been found to be related to greater sensitivity to subjective mood responses to nicotine via nasal spray in young adult never smokers.³²⁵ Specifically, Sensation Seeking Scale subscales of experience-seeking and disinhibition were associated with mostly pleasurable effects of nicotine (pleasant effects, head rush, vigor, and arousal), but also some aversive responses (tension, confusion). However, a subsequent, larger study related impulsivity and other factors associated with dependence risk to nicotine sensitivity in young adult nonsmokers²⁹⁰ and found only modest associations between one impulsivity factor—response disinhibition—and acute mood responses to nicotine (greater increases in anger and stimulated, blunted decrease in relaxation). History of other drug use and parental smoking history are unrelated to mood effects of nicotine via nasal spray.²⁹²

Mood effects of nicotine patch on nonsmoking adults appear to also vary as a function of “trait hostility,” another personality factor associated with greater risk of nicotine dependence in addition to its potential effects on onset, as noted earlier. Jamner and colleagues²¹⁵ found that nicotine, compared to placebo patch, prospectively decreased self-reported anger more among those high versus low in trait hostility. Notably, the same results were observed in smokers, suggesting that this association of trait hostility with anger reduction from nicotine does not moderate with chronic smoking exposure. High trait hostility was associated with high frequency of anger during placebo, suggesting that nicotine’s effects may be more pronounced in those with extreme baseline levels of response,

as has been found with other research on mood and behavioral responses to nicotine.³²⁶ Similar to this observation, animal research shows that nicotine attenuates startle response, a physiological measure associated with mood, to a greater degree in those with larger baseline startle magnitude.³²⁷

Physiological Indices of Affect

Description of Physiological Measures

of Affect. Mood is most commonly assessed via self-report measures, but some physiological responses related to affect include cardiovascular effects and startle response; several of these were outlined earlier and are listed in table 8.1. These same markers can be used to evaluate response to smoking as well as vulnerability to onset. Cardiac measures in this context (e.g., reward responsivity) are complicated by the fact that nicotine increases cardiovascular responses. However, it does not appear to modulate the effects of other influences on cardiovascular responses, such as acute environmental challenges.³²⁸ An alternative approach is to examine physiological startle—that is, the intensity of the eyeblink response to a sudden stimulus such as a sharp loud noise or electrical stimulation. The neurobiological significance of startle is discussed in chapter 9. Briefly, the magnitude of startle response is associated with the degree of negative affect reported by the person, and so, may index the negative affective limbic circuitry outlined earlier. Smoking and nicotine do not clearly alter startle response in dependent smokers or in nonsmokers,³²⁹ although some evidence indicates that nicotine attenuates startle in animals,³²⁷ as measured by whole-body startle response to the stimulus. However, nicotine influences the related measure of prepulse inhibition of startle, which is considered a measure of sensory processing rather than affect, and is discussed later. Regarding other physiological indices of affect, it has been noted earlier that electrodermal (skin conductance) and

electromyographic (muscle tension) measures are commonly obtained in studies of affective regulation, but few studies have examined responses to smoking or nicotine, and none (as far as is known) in nonsmokers administered nicotine.

Association with Dependence Risk.

There appears to be no evidence relating physiological indices of mood responses to nicotine to subsequent risk of nicotine dependence.

Heritability; Distribution of Responses in the Population. Research shows that startle response to low dose, but not moderate dose, nasal spray nicotine (i.e., curvilinear) was greater in those with the presence (versus absence) of the *DRD4*7*-repeat allele and in those with the *DRD2/ANKKI*CC* allele (versus **TC* or **TT* allele), but only among men and not women.²⁹³

Other Responses to Nicotine

No prospective studies have related onset of dependence to sensitivity to other responses to nicotine, likely for the same ethical and practical reasons noted above. Thus, this area will be only briefly noted. Effects of nicotine on these responses in chronic smokers are discussed in chapter 9. In addition, several of the variables listed below as important in the initial response to nicotine may also be considered factors that place an adolescent at risk for smoking initiation and subsequent progression. The description and rationale are outlined below for considering measures from various response domains as potential endophenotypes for risk of dependence.

Attention and Arousal. Smoking or nicotine typically helps prevent the deterioration in cognitive task performance over time in smokers, particularly when abstinent, but nonsmokers (i.e., testing of initial sensitivity to nicotine) have rarely been tested. However, in one interesting study,³³⁰ young adult nonsmokers were divided

into high- and low-baseline attention subgroups based on ADHD scales and given either a nicotine (7 milligrams [mg]) or placebo patch. Nicotine reduced errors of commission on the Conners' CPT in the low-baseline attention group, but impaired performance on another attention task, the Wisconsin Card Sorting Test, in the high-baseline attention subgroup. Thus, nicotine enhanced functioning only in those with weaker attentional control (and likely, lower arousal). As has been noted already, this characteristic is a risk factor for smoking onset; these data suggest it may be a risk factor that moderates a potential source of reinforcement from nicotine. This influence of nicotine as a function of baseline level of attention is consistent with results found in a few studies of mood, noted previously, and discussed elsewhere in greater detail.³²⁶

Electrophysiological Responses. As noted previously, startle response to a brief, loud tone assesses processes associated with affect. The degree to which startle is attenuated by a milder acoustic stimulus immediately preceding the tone is called prepulse inhibition (PPI) and indexes attention to sensory stimuli. Background on this measure is provided in detail in chapter 9. In one study of young adult nonsmokers administered low and moderate doses of nicotine via nasal spray,²⁹³ PPI tended to worsen (i.e., reduced inhibition of startle) in those with the *DRD2*C957T CT* (versus *TT* or *CC*) genotype (at the low dose only), with the absence of the *SLC6A3*9*-repeat allele, and with the *DRD2/ANKKI CC* (versus *TT* or *CT*) genotype (at the moderate dose only). Other individual difference characteristics, such as other drug use history or parental smoking history, are unrelated to PPI response to nicotine spray in nonsmokers.²⁹²

Impulsivity Via Cognitive Control and Approach Measures. Acute effects of nicotine on impulsive behavior can be assessed via variations on the stop/go

task, which as noted earlier, is an index of the frontal-striatal output control circuit, or by delay discounting, which is likely an index of the approach circuitry described earlier. Research examining initial sensitivity to nicotine's effects on each (i.e., in nonsmokers) is limited, but a few studies support the notion that these effects may promote dependence. In one study, nonsmoking adolescents with ADHD had improved stop/go responding (less disinhibition) following transdermal nicotine (7 mg), relative to placebo.²⁰¹ Methylphenidate, the standard medication to treat ADHD symptoms, also improved stop/go responding.

Cognitive Control and Executive Functioning. Several studies have looked at nicotine effects on measures conceived as tapping the cognitive-control circuitry described earlier. Cognitive function measures used in nicotine research are described in more detail in chapter 9. In terms of nicotine's effects on cognitive functioning upon initial exposure (i.e., initial sensitivity), little research shows clear improvement in such functioning. Exceptions include improvements in simple psychomotor tasks such as finger-tapping speed, perhaps reflecting gains in cognitive control, alertness, or arousal.³³¹ Research is mixed in terms of the performance of nonsmokers on more complex tasks, such as choice-reaction time speed.³³¹ However, short-term memory recall has been shown to be improved in nonsmokers by 2 mg of nicotine gum,³³² a 5-mg patch,³³³ or a 1-mg injection.³³⁴ Yet, memory recognition and delayed recall are impaired by 4 mg of gum,³³⁵ perhaps suggesting a nonlinear dose effect of nicotine on memory in nonsmokers.

The Stroop interference task is a measure of rapid information processing and cognitive control in that a rapidly activated dominant response must be suppressed in preference to a slower-activated nondominant response, producing a "conflict."³³⁶ It involves

activation of the anterior cingulate cortex, which is involved in the cognitive-control loop.³³⁷ Nicotine (7-mg patch), but not methylphenidate, improved performance on the Stroop task by reducing this interference in adolescents with ADHD, who had poor baseline performance.²⁰¹ However, smoking did not affect Stroop interference in light-smoking adolescents without ADHD,³³⁸ suggesting that nicotine's effects may be more apparent as baseline performance worsens. This is consistent with findings noted previously with regard to the influence of baseline on the observed effects of nicotine.

Finally, the Sternberg memory task is another rapid information processing task that requires subjects to briefly memorize one or a string of five target letters and then respond as quickly as possible to a new series of letter pairs in a way that indicates whether the given letter pair did ("hits") or did not ("correct rejections") contain a target letter. The difference in reaction time in milliseconds between the one- and five-letter trials ("D-prime") on items requiring correct rejection (involving processing of all target letters) is the primary measure of memory scanning speed (information processing).³³⁹ Although some studies show no clear effects of nicotine via nasal spray on performance of this task in nonsmokers,^{290,340} complex dose-related associations between *DRD4* genotypes and performance have been reported in nonsmokers.²⁹³

Nicotine Responses Assessed by Neuroimaging. Perhaps the most intriguing potential endophenotypes for initial nicotine sensitivity are effects of the drug on neurobiological changes, such as those revealed in neuroimaging measures (e.g., brain metabolic changes via positron emission tomography [PET]; blood flow changes in brain regions via fMRI). As emphasized above, CNS probes of the major neural circuits involved in behavioral risk markers may be promising

as endophenotypes for risk of onset as well as for the reinforcing effects of nicotine exposure. These tactics may prove to be particularly important for evaluating nicotine's effects on the brain in adolescence.

As is increasingly recognized, adolescence is a period of dramatic and ongoing neural development, particularly in circuits involved in cognitive control (the top-down control circuits described earlier). These circuits mature via myelination and pruning into early adulthood, probably in experience-dependent fashion. Further, such maturation is certainly moderated by sex hormones that are a major factor in adolescent development. Thus, one crucial direction for endophenotypes of exposure response may entail looking at alterations in the trajectory of brain maturation in response to nicotine exposure. Other research on initial nicotine effects (i.e., in nonsmokers) suggests that greater brain metabolic responses via 2-fluoro-2-deoxy-D-glucose (or FDG) PET are seen as a function of the personality factor of hostility.²¹⁶ As in the naturalistic research by Jamner and colleagues,²¹⁵ noted previously, the influence of trait hostility on brain metabolism due to nicotine was observed in smokers as well as in nonsmokers.

Initial Nicotine Sensitivity Endophenotypes: Summary and Future Directions

Nicotine Reinforcement and Reward

Nicotine reinforcement is the key process involved in the onset of dependence. Assessment of reinforcement at initial nicotine exposure is difficult, owing to ethical and practical problems with exposing naive individuals, especially youth, to nicotine. Moreover, there is not much evidence that variability in the reinforcing effects of initial nicotine exposure predicts

vulnerability to dependence. One objective measure of initial nicotine reinforcement—choice of nicotine or placebo—shows some concurrent validity with dependence, but choice in naive subjects has not been related to dependence vulnerability. However, animal research suggests that differential nicotine reinforcement emerges relatively quickly across early exposures. Thus, the trajectory of escalation in reinforcement across early exposures, rather than reinforcement at initial exposure, may hold promise as an index of dependence vulnerability (chapter 5). Age of initial smoking exposure is a strong predictor of smoking escalation and persistence but may have limited utility as an endophenotype. Nicotine reward is readily measurable in naive subjects via self-report and has been related to some genetic factors and other individual difference characteristics, including novelty seeking. Retrospective research suggests that liking of initial smoking is associated with greater subsequent dependence. Further support for this link is needed. Animal research on CPP and ICSS provides some potential avenues for development of more objective measures related to nicotine reward in humans.

Mood Effects and Other Responses to Smoking

Retrospective studies show with some consistency that greater pleasurable responses to initial smoking experiences, especially feeling “relaxed,” are associated with greater subsequent risk of nicotine dependence, largely supporting the sensitivity model of dependence vulnerability. Aversive responses to initial smoking appear to be unrelated to dependence vulnerability. On the other hand, the few prospective studies of acute nicotine administration in nonsmokers do not show robust mood effects, particularly pleasurable effects. This inconsistency in findings could be due to either biases in

retrospective self-reports or to the different populations studied. The retrospective studies included those who became dependent smokers as well as those with less smoking history, while the prospective studies of initial sensitivity involve only those who remained nonsmokers. A third possibility is that the retrospective studies examine responses to smoking, while the prospective studies examine responses to novel methods of nicotine administration, which are often more aversive than is smoking.³⁴¹ These methodological difficulties need to be controlled to verify that initial sensitivity to mood effects of nicotine predicts dependence vulnerability. Regarding other measures of mood and other responses to nicotine, research is too limited to determine whether any of these may be related to dependence risk.

Assessment of all of these responses in adolescents and relating these prospectively to risk of nicotine dependence would appear to minimize most sources of bias. However, this approach raises considerable ethical concerns, especially in youth who have never previously been exposed to nicotine. An alternative that may be ethical is to prospectively assess responses to acute smoking or nicotine in adolescents who have already begun to smoke, although such exposure almost certainly would be well after their initial exposure. Longitudinal research surveying adolescents regarding their self-report responses to smoking in general is being conducted.³¹⁷ Intermittent assessment of such responses prospectively, in laboratory-controlled studies of acute smoking exposure, could reveal more reliable and objective changes in acute responses that predict subsequent escalation of smoking to dependence.³⁴² Yet, as previously noted, the progression to daily smoking is not necessarily gradual and can occur quickly,³⁴³ leaving only a very brief window of opportunity for assessment of these responses to early smoking exposure.

Discussion of Future Directions

Numerous potential measures have been discussed in this chapter that may relate to nicotine dependence risk at or before initial exposure to nicotine. This final section will review some of the key conceptual and methodological issues that may need to be considered in future work examining such measures to establish endophenotypes that may inform genetic research on nicotine dependence.

Conceptual Issues

This chapter began by outlining a multilevel-analysis perspective on key neural systems related to smoking initiation and progression risk and attempted to identify low-level experimental measures, which are presumably closer to gene action, that may serve as endophenotypes for future studies. Data on the criteria for determining the validity of a putative endophenotype, such as heritability, reliability, and predictive validity, are limited for many of these candidate measures. This groundwork will need to be laid before these endophenotypic measures can be fully evaluated. A few measures have promising preliminary characteristics and may warrant more aggressive examination in relation to smoking initiation and progression risk. For example, cognitive control is a biologically well-studied ability anchored in the striatum and orbital and dorsal regions of the prefrontal cortex. It can be indexed via component cognitive measures as well as ERP measures. The predictive validity for specific measures is promising (i.e., P300 amplitude). Its heritability needs more study, but particular configurations (e.g., latent variable measures of response inhibition or set shifting) and measures (e.g., the P300) have strong heritability and deserve particularly close attention. A key gap is the extent of the understanding of the phenotypic and bivariate genotypic

associations of these measures with smoking onset risk.

Somewhat surprisingly, important measures of approach-related processes, such as delay discounting, reward cue detection, and other indicators of functioning of neural systems in the nucleus accumbens, orbital prefrontal cortex, and related ascending mesolimbic dopaminergic systems are little investigated with regard to precursive risk for later cigarette-use onset. Although many of these measures are related to smoking, it remains unclear whether alterations in these functions are risk factors for smoking, risk factors for persistence, or the consequences of smoking. This is important because some potential factors are likely to be present and measurable before the onset of tobacco exposure, and other factors predisposing to dependence in youth may only be observable in response to initial nicotine exposure. Therefore, in the second part of this chapter, the discussion moved to a more molecular level of analysis and considered a pharmacological perspective. In doing so, the available literature was reviewed on the processes that occur in the early stages of nicotine exposure that may increase the likelihood of further exposure to nicotine and the progression to nicotine dependence. There is not much evidence to support the notion that the reinforcing effect of initial nicotine exposure predicts vulnerability to nicotine dependence. However, nicotine-choice paradigms and trajectory of escalation in reinforcement across early exposures both hold promise as an index of nicotine dependence vulnerability. In addition, initial findings on the link between nicotine reward and subsequent development of nicotine dependence suggests that more research of reward is warranted.

As this chapter focused on potential endophenotypes for (1) smoking initiation and progression to nicotine-dependence risk and (2) the response to that initial

nicotine exposure, it was assumed that genetic influences on these points are at least partially distinct. Although initiation is an obvious prerequisite for progression and then dependence to emerge, it is likely that risks for initiation substantially involve both the general substance-use pathway and a specific pathway involving nicotine, whereas drug-specific factors may predominate in the initial response to nicotine. It is important to note that numerous factors place an individual at risk for smoking initiation, progression to regular smoking, and to nicotine dependence.⁴¹ Thus, smoking occurs in a psychosocial context, of which nicotine availability is a necessary but not sufficient condition. In focusing on endophenotypes for genetic risk for nicotine dependence, it is acknowledged that environment plays a large role in who exposes themselves to nicotine via cigarette smoking and who continues irrespective of their initial smoking experience or their genetic susceptibility.

It is suggested here that both general and specific genetic risk factors have to be targeted via endophenotype studies. These genetic risk pathways are probably not completely independent of one another. Indeed, similar and unique neural circuitry may be involved in smoking initiation risk and in response to initial nicotine exposure. For example, reduction in reward may be particularly important as a reinforcer for initial nicotine exposure response, whereas breakdowns in cognitive control and attentional regulation may be crucial to smoking initiation and progression. Conversely, similar operations may be involved in both smoking initiation risk and initial nicotine exposure response. For instance, approach systems may contribute to an adolescent exploring nicotine use, and reactivity of that same system may contribute to reinforcing properties of nicotine upon exposure. As such, the discrete treatment of these nicotine-dependence phenotypes in this

chapter is heuristic. However, such analytic treatment may be necessary to identify mechanisms, and potential, unique genetic influences, at each inflection point.

It is important to note that the smoking initiation and progression risk variables have been framed through a neurobiological temperament model that permitted a multilevel analysis beginning with surface behavioral traits, and proceeding to lower-level laboratory measures as candidate endophenotypes, perhaps getting closer to gene action. Of course, whether or not something is “closer to the gene” is an empirical question. Some seemingly simple markers may in fact be genetically complex (e.g., it is not clear that “attention” as measured on a cognitive task is genetically simpler than nicotine dependence as measured in a structured interview). Here there is no claim to genetic simplicity for any of these candidates: each will require evaluation with respect to the criteria set forth to support the likelihood that a measure is an endophenotype. Likewise, temperament and personality variables, such as novelty seeking, may indeed be endophenotypes (mediators) that are genetically more complex than nicotine-dependence phenotypes. These trait variables also may serve as moderators as well as diathesis variables; their specific role will depend on the specified conceptual and statistical model. These types of conceptual issues are highlighted in chapter 3.

Under the premise of multiple pathways, a given endophenotype should capture a subset of the population (just as will a given genotype). Thus, a relative with little exposure to nicotine may appear similar to a nicotine dependent smoker on a putative endophenotype. That is, not all adolescents who have initiated smoking and progressed to nicotine dependence will have a particular endophenotype, and not all adolescents with an endophenotype will have initiated smoking and progressed to nicotine

dependence. Likewise, the evaluation of endophenotype-by-endophenotype interactions may (1) help to identify genetic signals across multiple pathways, which at a more surface level may reflect interactions of the biological and traitlike systems, or (2) aid in understanding why endophenotypes are present in adolescents who initiate smoking experimentation but do not progress to nicotine dependence.

The search for endophenotypes for nicotine-dependence risk at or before initial nicotine exposure will likely raise important issues with respect to smoking phenotypes, endophenotypes, and their distinction. If a smoking phenotype is weak, this may negatively affect statistical models designed to link genes to endophenotypes to phenotypes. An important question is whether phenotypic definition is improved by clarifying candidate endophenotypes. Effective endophenotypes may inform phenotype definition (e.g., smokers who have strong PET response to nicotine compared to those who do not) in the future. Likewise, the conceptual distinction between an endophenotype and a “refined phenotype” is murky. For example, rate of smoking escalation could be considered a phenotype as well as an index of an endophenotype (reinforcement) for nicotine exposure.

Methodological Issues

Methodological problems in identifying and measuring liability in those who have not yet initiated smoking are not trivial.^{39,40} Yet, measuring endophenotypes for nicotine-dependence risk in the context of prospective designs are crucial to establishing predictive validity as well as the utility of this approach. For example, prospective observational cohorts usually rely on a sufficiently large number of youth (general population or those at risk) measured repeatedly across time. A majority of the endophenotype measures are laboratory

based and possibly time variant. Thus, recruiting and retaining youth in studies involving the completion of laboratory-based tasks (endophenotype measures) on several occasions across time can be challenging. In addition, as noted in the second part of this chapter, there are methodological concerns with innate sensitivity research. For the retrospective studies, these include the definition of “initial” exposure, the reliance on retrospective reports of smoking experiences, and the unknown role differential nicotine dosing during initial exposure may play in determining differences in self-reported sensitivity to that exposure. For prospective studies, concerns include ethical dilemmas surrounding administering nicotine to naïve adolescents, generalizability of novel nicotine delivery methods to smoking, whether nicotine sensitivity is consistent from adolescence to young adulthood, and self-selection biases associated with the willingness to be exposed to nicotine through research.

Despite these methodological challenges, such studies could potentially offer comprehensive directional models that include surface characteristics, endophenotypes, and genes, which would provide support for one or more endophenotypes as mediator of the genetic effects on a nicotine-dependence phenotype. The endophenotype(s) should mediate the association between the candidate gene and the phenotype, indicating that the effects of a particular gene are expressed, fully or partially, through the endophenotype(s).¹³ These types of models have been proposed in studies investigating endophenotypes for the genes that underlie psychiatric disorders. As far as is known, only a few studies have evaluated these types of models with respect to nicotine-dependence risk phenotypes.^{21,24} More complex relationships may also be possible. For example, a gene may have a delayed effect on a phenotype, which is not evident until a particular developmental period (e.g., mid to late adolescence,

late adolescence to young adulthood). In addition, a suppressor effect may be present (e.g., genotype is positively related to the endophenotype and the phenotype, but the endophenotype is negatively related to the phenotype). In this situation, a simple assessment of the indirect effects to total effects may lead to the erroneous conclusion that the endophenotype does not account for the relationship between the genotype and the phenotype.^{344,345} In addition to mediation, the endophenotype should moderate association between the candidate gene and the phenotype, indicating that the effects of a particular gene are stronger in individuals with a phenotype who also show the endophenotype.¹³

With respect to analytic approaches, one must also consider the utility of using a latent variable as an endophenotype measure; that is, endophenotypes are latent (factors), rather than observed, and are comprised of several indicators (more than one endophenotype measure). This has been found to strengthen heritability coefficients,^{234,235} an important criterion for validating endophenotypes. However, it is unclear whether a composite measure renders the endophenotype more complex than the phenotype it is indexed to and is, therefore, less genetically simple. This approach has not yet been attempted to evaluate endophenotypes for smoking initiation, progression, and the initial response to nicotine.

Summary

This chapter has described potential endophenotypes for nicotine-dependence risk at or before initial nicotine exposure. The available literature points to several promising endophenotypes and highlights the limited research on the validity of putative endophenotypes. This research foundation will need to be built before the utility of the endophenotype approach can be

evaluated. While an endophenotype approach may help close the explanatory gap between candidate genes and the onset of nicotine dependence, it relies on conceptually and methodologically well-grounded research.³⁴⁶ A conceptual framework has, therefore, been emphasized that could guide future studies, including the selection of endophenotypes, and enable the integration of research on specific endophenotypes for nicotine-dependence risk and general substance-abuse endophenotypes.

Conclusions

1. Several higher-order psychological constructs can consolidate many smoking initiation and progression risk variables. These constructs, as well as sensitivity to initial nicotine exposure, can be related to observable neural, physiological, and behavioral measures that may, in turn, serve as potential candidate endophenotypes for genetic research on nicotine dependence.
2. Several laboratory measures exist that could be associated with the risk for smoking initiation and progression and subsequent nicotine dependence, but these associations have yet to be investigated. Findings are mixed for the reliability and heritability of these measures, and minimal evidence exists for their validity, representing an area for further study.
3. Measurement of sensitivity to initial nicotine exposure is subject to numerous methodological limitations, including ethical difficulties with empirical measurement in naive (e.g., previously unexposed to nicotine) subjects, a lack of consideration of smoking dose and context from retrospective self-reports, recall bias, and self-selection to early smoking experience. At the same time, preliminary findings indicate that measures of reward and mood effects surrounding initial exposure to smoking show promise as a potential basis for endophenotypes of a genetic predisposition to nicotine dependence.
4. The available evidence points to the plausibility of endophenotypes that link factors at or before initial nicotine exposure with the potential for nicotine dependence. These endophenotypes reflect approach, avoidance, and control-related traits as well as initial sensitivity and exposure measures in response to nicotine intake. Further research is needed to help identify endophenotypes that connect risk variables for nicotine dependence to genetic influences.

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