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Incorporating Social Context into Genetic Studies of Nicotine Dependence

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Tobacco use takes place within a social context that has been shown to interact with genetic factors to influence the definition and measurements of phenotypes and endophenotypes for nicotine dependence. This chapter examines available research and future trends related to social context factors that could inform subsequent genetic studies of smoking, including

- *Macrocontextual factors ranging from distal measures such as culture and socioregional factors to more proximal measures such as detailed data on socioeconomic status*
- *Microcontextual factors such as smoking in specific interpersonal relationships, including findings from the Nonshared Environment in Adolescent Development Project studying twins and siblings*
- *Integrated proximal indicators of both macro- and microcontext such as ecological momentary assessment*

Available evidence indicates that social context can have a clear impact on the heritability of smoking and many of its component traits. There is a growing case for such gene-environment interplay to become part of a broader matrix of etiological architectures employed in future genetic research on nicotine dependence.

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Introduction

This chapter focuses on *why* the incorporation of social contextual influences could represent a core strategy for genetic studies of nicotine dependence—a complex phenotype that arises within socially defined (and in some cases socially controlled) contexts[1]—and *how* newer methodologies can be used to gain better traction on social contextual influences. The emphasis is on "social contextual" rather than "environmental" influences because the environment in the behavioral genetic paradigm includes any factor that is not, strictly speaking, heritable (and thus may include an extraordinary range of potential etiological contributors including biological influences). The working approach to social context taken in this chapter is simply to consider a small range of factors, typically thought of as part of the social environment, that represent putative influences on the developmental pathways to nicotine dependence and that have been, or could easily be, considered in either behavioral or molecular genetic research. The focus is on specific examples of social contextual factors that have received some attention in genetic designs to illustrate the conceptual grounding that guides such work, as well as provide examples of specific methodologies that are used to intensively measure these constructs. The broader point to be taken from these examples, however, is that social context matters, and that the full range of potent social influences should be taken seriously in genetic research on nicotine dependence by using the appropriate methodologies to bring these factors into genetically driven research.

As discussed in chapter 3, multiple levels of phenotypes contribute to and compose the construct of nicotine dependence. Similarly, a multitude of factors make up the social context, from the macro level (e.g., sociopolitical) down to the micro level (including psychosocial influences such as interpersonal relationships). This chapter focuses on selected examples of such macro and micro social factors of particular relevance to smoking phenotypes; the goal is to illustrate both concepts and methods rather than provide an exhaustive review.

Some behavioral genetic studies of tobacco use have used the phrase *genetic architecture* when describing the pattern of heritable influences that may be observed via genetically informative designs such as the twin paradigm.[2] This construct appeals because the expression of genetic systems is assumed to contribute to the structural foundations of complex phenotypes, such as the range of behaviors that involve use of tobacco. The descriptive statistic heritability typically is offered as a proxy for the overall strength of genetic contribution to a phenotype, and in this approach, is used to give some guidance to the phenotypes that most strongly reflect underlying genetic effects.[3] Thus, "genetic architecture" has been used to describe the underlying heritability of one (univariate) or multiple (multivariate) indices of smoking, such as age at initiation, amount smoked, and smoking cessation attempts.[2]

This chapter broadens the concept by focusing on "etiological architecture" to serve as a reminder of a number of principles that have long been acknowledged in behavioral genetics.[3] The typical components of behavioral genetic models (heritability, common or shared environment, nonshared or unique or individual-specific environment) are estimates of the mix of etiological influences on phenotypic moving targets that reflect a host of factors, including the population studied (embedding both geographical and temporal characteristics), the definition as well as measurement of the phenotype, and the extent to which environmental influences have been measured and modeled. In this sense, "etiological

architecture" refers to the dynamic mix of genetic and nongenetic influences on phenotypes captured in particular periods and within specific social contexts. This point emphasizes that the understanding of genetic foundations of behavior undoubtedly can (and will) change as methods for measuring phenotypes, genotypes, *and* nongenetic (or "environmental") influences are refined. The "architecture" of smoking behaviors is not a firm foundation but rather a pliable blueprint of how to evaluate the role of genetic and nongenetic influences on particularly defined phenotypes—defined not just in terms of psychometrics but also as expressions of measurable behavior, in particular, historical, geographical, and social contexts. As a result, a primary goal of both quantitative and newer molecular methodologies is not only to get the phenotypic targets as well defined and measured as possible to move closer to "true" indicators and sequelae of gene expression but also to understand how gene expression operates in conjunction with, and in response to, a range of nongenetic influences.

The focus on social contextual influences in genetic studies certainly reverberates and builds upon the interest in gene-environment interplay in behavioral science,[4–6] and specifically as applied to drug use,[1] which is the focus of chapter 3. The idea of bridges between genetic effects on phenotypes and environmental influences has been a theme in behavioral genetics for decades. This theme has taken on new momentum with the application of a number of novel methodologies and strategies, including an emphasis on both "measured genes" (molecular genetic markers such as candidate gene polymorphisms) and "measured environments" (inclusion of environmental variables in genetic analyses) as well as expansions of behavioral genetic paradigms, as shown in studies by Moffitt and colleagues.[4–6] These papers make very explicit the utility of directly incorporating environmental measures into genetic studies, the theoretical models that capture a variety of means by which genes and environment come together in producing clinically meaningful phenotypes, and the design strategies for achieving appropriate opportunities to examine the joint effects and interplay between genes and environment. Given this, the advances (as evidenced in the series of papers cited above, along with chapters 3 and 4) were chosen as a platform to consider how social contextual influences have been, and may be, incorporated into genetic studies of nicotine dependence. In particular, this chapter focuses on areas that have some empirical basis in terms of incorporating social context into genetically informative designs of tobacco use; it then considers newer methodologies that may provide even greater traction in future studies.

Why Incorporate the Social Context?

Most behavioral genetic studies have generated parameter estimates of genetic and environmental influences by using the fundamental quantitative genetic model, which does not incorporate actual (or "measured") aspects of the environment.[3] Why is it important to consider this? A first key issue is that the "unmeasured" genetic and nongenetic effects generated in the traditional model are assumed to be *additive* in nature and are calculated as such. There is, thus, typically limited (or no) opportunity to detect statistical evidence for gene-environment interplay without utilizing alternative genetic designs (such as the Children-of-Twins design, or COT) in that the two primary forms of gene-environment interplay—gene-environment interaction and gene-environment correlation—are embedded within the additive genetic component and contribute to the overall estimation of heritability. Second, without the inclusion

The Classic Quantitative Genetic Model and Smoking Behaviors

In framing the potential utility of incorporating the social context in genetic studies of smoking, it is necessary to briefly consider the core work in behavioral genetic studies. As discussed in chapter 6, a number of genetically informative studies have examined a range of smoking phenotypes. Indeed, since a landmark paper by Carmelli and colleagues[a] provided evidence for the heritability of smoking by using the classic twin method, a number of twin studies have focused on varying levels of smoking intensity, including smoking initiation (e.g., ever puff versus never puff) and smoking frequency during adolescence[b,c,d,e,f,g,h,i,j,k,l] as well as smoking persistence/regular smoking and nicotine dependence.[m,n,o,p,q,r]

As discussed in reviews by Sullivan and Kendler[s] and Li and colleagues,[t] the relative mix of genetic and environmental factors appears to be different for different levels of smoking intensity. Li and colleagues[t] have determined, using meta-analysis, that smoking initiation is influenced significantly both by genetic factors (with heritability estimates of 0.37 ± 0.04 for males and 0.55 ± 0.04 for females) and by shared environmental (nongenetic influences that operate to produce similarity in family members) factors (0.49 ± 0.04 for males and 0.24 ± 0.06 for females). Li and colleagues[t] also provide evidence of substantial heritability of smoking persistence (0.59 ± 0.02 for males and 0.46 ± 0.12 for females), with shared environmental influences being more prominent for females (0.28 ± 0.08) than for males (0.08 ± 0.04). Sullivan and Kendler[s] reached somewhat similar conclusions, suggesting substantial heritability of smoking initiation (approximately 0.60), along with significant shared environmental influences (approximately 0.20), with genetic factors being primarily responsible (heritability of approximately 0.70) for the transition to nicotine dependence and with less impact observed from shared environmental influences. Both continuities and discontinuities in the genetic effects on smoking initiation and progression to higher levels of smoking intensity are being evaluated with quantitative approaches such as those discussed in chapter 6.

[a]Carmelli, D., and G. E. Swan. 1995. Genetic and environmental influences on tobacco and alcohol consumption in World War II male veteran twins. In *Alcohol and Tobacco: From Basic Science to Clinical Practice* (NIAAA Research Monograph No. 30), ed. J. B. Fertig and J. P. Allen, 89–106. Bethesda, MD: U.S. Department of Health and Human Services.

[b]Boomsma, D. I., J. R. Koopmans, L. J. Van Doornen, and J. F. Orlebeke. 1994. Genetic and social influences on starting to smoke: A study of Dutch adolescent twins and their parents. *Addiction* 89 (2): 219–26.

[c]Han, C., M. K. McGue, and W. G. Iacono. 1999. Lifetime tobacco, alcohol and other substance use in adolescent Minnesota twins: Univariate and multivariate behavioral genetic analyses. *Addiction* 94 (7): 981–93.

[d]Koopmans, J., A. Heath, M. Neale, and D. Boomsma. 1997. The genetics of initiation and quantity of alcohol and tobacco use. In *The genetics of health-related behavior,* ed. J. R. Koopmans, 90–108. Amsterdam: Print Partners Ipskamp.

[e]Koopmans, J. R., W. S. Slutske, A. C. Heath, M. C. Neale, and D. I. Boomsma. 1999. The genetics of smoking initiation and quantity smoked in Dutch adolescent and young adult twins. *Behavioral Genetics* 29 (6): 383–93.

[f]Maes, H. H., M. C. Neale, N. G. Martin, A. C. Heath, and L. J. Eaves. 1999. Religious attendance and frequency of alcohol use: Same genes or same environments: A bivariate extended twin kinship model. *Twin Research* 2 (2): 169–79.

[g]McGue, M., I. Elkins, and W. G. Iacono. 2000. Genetic and environmental influences on adolescent substance use and abuse. *American Journal of Medical Genetics* 96 (5): 671–77.

[h]Rende, R., C. Slomkowski, J McCaffery, E. Lloyd-Richardson, and R. Niaura. 2005. A twin-sibling study of tobacco use in adolescence: Etiology of individual differences and extreme scores. *Nicotine and Tobacco Research* 7 (3): 413–19.

[i]Rhee, S. H., J. K. Hewitt, S. E. Young, R. P. Corley, T. J. Crowley, and M. C. Stallings. 2003. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Archives of General Psychiatry* 60 (12): 1256–64.

[j]Slomkowski, C., R. Rende, S. Novak, E. Lloyd-Richardson, and R. Niaura. 2005. Sibling effects on smoking in adolescence: Evidence for social influence from a genetically informative design. *Addiction* 100 (4): 430–38.

[k]Stallings, M. C., J. K. Hewitt, T. Beresford, A. C. Heath, and L. J. Eaves. 1999. A twin study of drinking and smoking onset and latencies from first use to regular use. *Behavior Genetics* 29 (6): 409-421.

[l]White, V. M., J. L. Hopper, A. J. Wearing, and D. J. Hill. 2003. The role of genes in tobacco smoking during adolescence and young adulthood: A multivariate behaviour genetic investigation. *Addiction* 98 (8): 1087–1100.

[m]Heath, A. C., N. G. Martin, M. T. Lynskey, A. A. Todorov, and P. A. Madden. 2002. Estimating two-stage models for genetic influences on alcohol, tobacco or drug use initiation and dependence vulnerability in twin and family data. *Twin Research* 5 (2): 113–24.

[n]Kendler, K. S., M. C. Neale, P. Sullivan, L. A. Corey, C. O. Gardner, and C. A. Prescott. 1999. A population-based twin study in women of smoking initiation and nicotine dependence. *Psychological Medicine* 29 (2): 299–308.

[o]Madden, P. A., A. C. Heath, N. L. Pedersen, J. Kaprio, M. J. Koskenvuo, and N. G. Martin. 1999. The genetics of smoking persistence in men and women: A multicultural study. *Behavior Genetics* 29 (6): 423–31.

[p]Madden, P. A., N. L. Pedersen, J. Kaprio, M. J. Koskenvuo, and N. G. Martin. 2004. The epidemiology and genetics of smoking initiation and persistence: Crosscultural comparisons of twin study results. *Twin Research* 7 (1): 82–97.

[q]Maes, H. H., P. F. Sullivan, C. M. Bulik, M. C. Neale, C. A. Prescott, L. J. Eaves, and K. S. Kendler. 2004. A twin study of genetic and environmental influences on tobacco initiation, regular tobacco use and nicotine dependence. *Psychological Medicine* 34 (7): 1251–61.

[r]Vink, J. M., G. Willemsen, and D. I. Boomsma. 2005. Heritability of smoking initiation and nicotine dependence. *Behavior Genetics* 35 (4): 397–406.

[s]Sullivan, P. F., and K. S. Kendler. 1999. The genetic epidemiology of smoking. *Nicotine & Tobacco Research* 1 Suppl. 2: S51–S57, S69–S70.

[t]Li, M. D., R. Cheng, J. Z. Ma, and G. E. Swan. 2003. A meta-analysis of estimated genetic and environmental effects on smoking behavior in male and female adult twins. *Addiction* 98 (1): 23–31.

of specific nongenetic/environmental variables, no information is gleaned on how the effect sizes of the descriptive statistics generated in the quantitative genetic model (heritability, shared environment, nonshared environment) may change under varying environmental conditions.

These considerations are important for any clinical phenotype but take on added importance for substance-use behaviors, including smoking, which are defined in part by availability of and exposure to the substances in the environment. Merikangas and Avenevoli[7] have described how the traditional genetic epidemiology triangle, which focuses on host susceptibility, environmental factors, and exposure to a disease-causing agent, is particularly well suited to the study of substance use. In this model, exposure to the source of nicotine (e.g., a cigarette) would be the primary agent that is a necessary condition for development of nicotine dependence, and both exposure to the agent and reaction to the agent would reflect joint influences of host factors as well as environmental factors. In this regard, environmental factors including cultural forces (such as norms against women smoking), protobacco promotional activities, antitobacco activities (e.g., smoke-free environments), and proximal interpersonal influences (e.g., influences of parents, siblings, and friends) need to be integrated into the genetic epidemiology triangle to understand how they directly shape the expression of host/genetic susceptibility to nicotine dependence. These joint effects thus imply complex layers of potentially connected factors, as described by Eaves[8] and quoted by Lessov and colleagues:

> To the degree that drug-use behavior is heritable, inherited liability toward drug

> use or misuse increases the risk for drug-use behavior but it does not lead to or cause drug use. The expression of genetic liability (i.e., substance use and misuse) depends on environmental conditions. For example, exposure of the organism to a drug is necessary. Exposure, in turn depends on other environmental factors such as drug access and availability, which is related to neighborhood, home, and peer group environment, to name a few. People mistakenly think that "Everything is genetic," ignoring that while an individual does not have control over their *[sic]* genetic makeup, an individual is in constant dynamic interaction with their *[sic]* environment; and it is that interaction that contains powerful information about the probability of drug use and misuse.[1(p1519)]

These perspectives from genetic epidemiology overtly posit that interaction between (potentially nested) levels of host, environment, and agent variables underlie substance use and, in particular, progression to problematic levels of use (such as nicotine dependence). Within this framework, both measurement of environmental factors and inclusion of these factors in the analytic models would be necessary for a complete understanding of the genetic effects on nicotine dependence. The traditional quantitative genetic model, with emphasis on additive genetic and environmental effects, along with no attention to measured sources of environmental influence, does not provide an optimal opportunity to delve into the purported interplay between agent, host, and environment. Rutter and colleagues[6] have provided a comprehensive review of the multiple models of gene-environment interplay, and these models provide a platform for considering alternatives to the additive genetic model. Of particular relevance are major classes of gene-environment interplay, reviewed by Rutter and colleagues[6] (see also Shanahan and Hoffer[9]), which include (1) variations in genetic influence according to environmental circumstances; (2) gene-environment correlations; and (3) gene-environment interactions.

Behavioral Genetic Studies of Smoking That Incorporate Social Context

Although the behavioral genetic literature has primarily relied upon the application of biometrical models to data on cigarette use, examples from newer studies incorporate social contextual measures. These studies provide empirical foundations for the speculations offered above, and this section reviews pertinent studies. For heuristic purposes, both "macrocontextual" indicators of social context—constructs of influence that range from broad cultural expectations to more localized geographic effects—as well as "microcontextual" influences[10] that reside closer to individual-level factors, such as interpersonal relationships, will be used. In particular, specific social contextual variables that have been studied by using the behavioral genetic paradigm will be referenced. All the studies to be reviewed rely on modeling types of gene-environment interaction by using extensions of the fundamental biometrical model of quantitative genetics via the inclusion of a specified, measured environmental factor that can be tested as a moderator of the latent genetic effect (as well as the latent, shared environmental effect). The rationale for this approach, along with some of the methods that may be used, is discussed in Turkheimer and colleagues[11] and Purcell and Koenen;[12] see also Kendler and colleagues[13] and Timberlake and colleagues[14] for inclusion of moderators in biometrical models of smoking. The key propositions tested, using the nomenclature from Rutter and colleagues,[6] are the following:

- Are there environmental factors that reduce the impact of genetic influences?
- Are there environmental contexts that, in contrast, especially accentuate genetic influences?

Macrocontextual Factors as Moderators of the Etiological Architecture of Smoking

It is well documented, and beyond the scope of this chapter, that population levels of cigarette use have been heavily influenced by many dynamic social factors that have changed over the decades, including tobacco control and prevention initiatives.[15] The focus here is on the extent to which *behavioral genetic studies* have incorporated such macrocontextual factors into the biometrical modeling approach. Two points should be noted. First, these studies provide examples of the utility of incorporating macrocontextual factors into genetically informative studies of tobacco use and nicotine dependence. Second, these studies also highlight how limited this research has been, given the wide range of macrocontextual factors that *could* be incorporated into quantitative genetic paradigms. Thus, the studies reviewed below demonstrate how the expression of genetic liability to smoking may be shaped by the larger social culture (e.g., how the effects of genes change over time in concert with social changes or vary within populations that vary on macrosocial indices) and highlight approaches that can be used in future studies to integrate potent macrosocial influences.

Effects of Culture and Cohorts

One concrete and dramatic example comes from investigations into the etiological architecture of cigarette smoking in China. Lessov-Schlaggar and colleagues[16] reported that within a sample of 1,010 adult Chinese twins, 58% of the male twins were smokers, but over 99% of female twins were nonsmokers. Whereas the etiological architecture of smoking in male twins was similar to that reported in studies from other cultures, there were no individual differences in female smoking to model. An examination of changes in heritability based on cohort effects from the population-based Swedish Twin Registry expands this theme.[17] Rates of regular tobacco use in women born before 1925 were low and found to be environmental in origin; in contrast, as smoking rates increased in women born after 1925, heritability estimates increased. This finding serves as a reminder that the macrocontext can have overwhelming impact on the choice or ability to use cigarettes that can fundamentally nullify or promote net genetic effects, and it reinforces the suggestion that the etiological architecture of smoking *must* be defined by reference to the social context in which it is observed.

Less dramatic, but nonetheless important, examples from behavioral genetic studies of smoking have attempted to account for differences across either cultures or birth cohorts. In 1993, Heath and colleagues[18] demonstrated that the decline in smoking in more recent birth cohorts did not affect the estimates of genetic and environmental influence on smoking initiation. They did find, however, differences in the heritability and shared environmental estimates in Australian versus U.S. samples. A subsequent study suggested that cultural background may influence the magnitude of shared environmental effects on lifetime smoking but that estimates of both genetic and environmental effects on smoking persistence were unaffected by culture.[19]

Socioregional Influences

The few twin studies mentioned above have provided tests of a particular type of gene-environment interaction by using distal environmental measures[4,5] and latent

genetic factors inferred by the comparison of monozygotic and dizygotic twins. Although some of the results reflect profound social contextual effects (e.g., cultural discouragement of smoking in females in China), the studies examining cross-cultural differences introduce the possibility of examining more subtle differences that may exist within cultures that would not be detected without overt measurement of possible sources of environmental influence. Surprisingly, no behavioral genetic studies of smoking have used this strategy. The potential utility of this approach is illustrated by research on adolescent alcohol use in Finland. Rose and colleagues[20] made the important observation that regional residency (urban versus rural) significantly moderated genetic effects on drinking patterns, including longitudinal change in drinking observed over a 30-month period. Specifically, genetic effects were larger within the sample of adolescents who resided in urban areas, and shared environmental factors were larger for the subsample living in rural areas.

Two important points are raised by the work of Rose and colleagues.[20] First, it demonstrates that socioregional variations can be detected and modeled within the behavioral genetic paradigm and that such social contextual factors can have a large influence on the etiological architecture of substance use. Second, these authors took the important step of incorporating more specific measures of socioregional influences into their analyses—namely, the relative proportion of young adults in a regional area, the frequency of migration in and out of a region, and the relative amount of money spent on alcohol in an area.[21] When these more specific social contextual measures were introduced into the biometrical models, clear evidence of gene-environment interaction was found. Both a higher proportion of young adults and higher migration levels were associated with stronger genetic effects on drinking patterns in adolescents, whereas lower levels of young adults and migration yielded greater shared environmental influences.

As discussed by Dick and colleagues,[21] variation in these social structures can either promote genetically influenced individual differences in drinking (via more opportunities with peers and less stable social structure) or mask genetic differences (as the strength of shared environment increases with more stability and less opportunity for peer influence). The more general point of this work, as noted by the authors, is that they moved from the more distal index of residential residence (urban versus rural) to potential proximal indicators of social context that may reside closer to actual mechanisms of influence. This important theme of translating distal environmental measures into more proximal indicators[4,5] will be revisited in the following section on newer methodologies for examining social context—and certainly carries forward the theme of attending to multiple levels of assessment of both smoking-related phenotypes (chapter 3) and environments.

Microcontextual Factors as Moderators of the Etiological Architecture of Smoking

As noted above, social contextual factors may be conceptualized as operating at multiple levels, with the final important pathway being a proximal end point reflected at the individual level. As these microcontextual features that are more individually based are considered, the primary focus is on interpersonal influences, which have received attention in some behavioral genetic papers. Interest in interpersonal dynamics came about, in part, because of concern that contact between twins could violate the equal environments assumption (EEA) (if the level of contact was greater for monozygotic as compared to dizygotic twins). That is, as the twin

method attributes greater similarity (or concordance) of monozygotic versus dizygotic pairs to differences in genetic relatedness (and hence heritability), uncontrolled nongenetic factors that promote differences based on zygosity may artificially inflate heritability estimates. For example, Kendler and Gardner[22] found that the heritability of smoking initiation was reduced by about 10% after controlling for the higher degree of social contact in monozygotic pairs as compared to dizygotic pairs. Kendler and colleagues[23] also reported that their data were consistent with modest influences of social contact between twins (and the violation of the EEA) on nicotine dependence. Later evidence suggests that the socialization effects that differ between monozygotic and dizygotic twins may influence smoking initiation to a much larger degree than does smoking persistence.[19,24] These effects may also differ based on gender. Hamilton and colleagues[25] found strong moderation via social contact of both shared environment (which increased) and heritability (which decreased) in female, but not male, twin pairs.

The implications of these studies go beyond the extent to which heritability estimates may, or may not, be biased by violations of the EEA. Of more substantive interest is the extent to which interpersonal dynamics may influence smoking behavior as a form of social influence, which may operate both as a main effect (i.e., independent of genetic relatedness) as well as in combination with genetic factors. As discussed earlier, the robust shared environmental effects found for smoking initiation suggest potential socialization effects that could derive in part from peers and siblings.[26] Vink and colleagues[27] approached this issue using a twin-family design. They examined the extent to which current smoking behavior was associated with the smoking behavior of peers and siblings (along with parents and spouses). Using a cross-sectional design, they found strong evidence of both peer and sibling effects on smoking in adolescence; these effects were not seen for smoking in adulthood. Rather, in adulthood, the most important relational predictor of smoking was zygosity of co-twin smoking (such that having a monozygotic twin who smoked conveyed the most prediction of current smoking status). They concluded that social effects may be most evident in adolescence, but lessen in importance in adulthood, when genetic factors become a stronger influence on the likelihood of smoking. Taking this a step further, there is also evidence that exposure to smoking by parents and peers in adolescence and early adulthood, when accounted for in the traditional biometrical model, substantially *reduces* the impact of genes on smoking behavior, leading to the suggestion that environmental factors provide the strongest influence on smoking during these developmental periods.[28]

Subsequent expansions of this focus on interpersonal influences have focused on direct sibling effects by utilizing more differentiated measures of the sibling relationship as well as extension of the twin paradigm to include siblings of varying genetic relatedness (full, half, and unrelated siblings) via the genetically informative subsample of the National Longitudinal Study of Adolescent Health (Add Health).[29,30] A first finding[29] is that monozygotic twins have elevated levels of time spent together (social contact) as well as mutual friendships as compared with all other sibling types. However, the interpretation of this finding is not straightforward. Levels of social contact and mutual friendships did not follow a dose-response association with zygosity once the effect of monozygotic twins was considered. Thus, it may be that monozygotic twins, compared with all other sibling types, have much more commonality in their time spent with each other as well as with friends.

That said, the inflated monozygotic concordance for time together and mutual

friendships did not alter the estimates of heritability of smoking frequency (measured as number of days smoked over the last 30 days). Rather, time spent together and mutual friendships both significantly moderated the shared environmental component.[29] These two variables were also analyzed along with amount of sibling affection to create a construct of sibling connectedness, which also moderates the shared environment effect but not the estimate of heritability.[30] The finding that twins and siblings form connections with mutual friends, and that these social groupings represent social rather than genetic influences on smoking, highlights the importance of considering broader effects of larger social networks as a potent influence on smoking patterns.[31,32]

Summary

Overall, the studies reviewed in this section provide a good starting point for considering how social contextual factors may be integrated into genetically informative designs. These studies provide solid empirical evidence that the estimation and interpretation of the descriptive statistic of heritability can vary when referenced according to important macro- and microcontextual factors and represent a good starting point for a more realistic genetic epidemiological model of smoking.

Proximal Measures of the Social Context

It has been suggested that moving from distal indicators of the social environment to more proximal measures will be important for improving the resolution of models of gene-environment interplay.[4–6] Building on this suggestion, the realization of adequate tests of these models will depend in part on careful and forward-looking assessment of candidate social contextual factors (as one class of environmental factors in models of gene-environment interplay). It is becoming recognized that accurate measurement of the environment is as critical to the success of any foray into gene-environment interplay as is quality control of genotyping.[6] Despite this recognition, there has been a tremendous disparity in the attention and resources given to "molecular" assessment of the environment in genetic studies as compared with the effort devoted to dissection of the genome,[5] despite the strong evidence on the potent effects of a number of social contextual factors. These include social networks as well as the overarching social and cultural environment, which includes pro- and antitobacco factors.[31,32]

Dissemination of the multiple levels and corresponding constructs of social context that could bear upon smoking and nicotine dependence would require a separate monograph devoted to that purpose. In lieu of that, this section will build on the candidate social contextual factors reviewed in the prior section by illustrating newer methodologies that attempt to capture proximal social contextual influences that could be integrated relatively easily into most genetically informative designs.

In general, behavioral genetic studies are very well positioned to incorporate both macro- and microcontextual measures, and two particular features can be exploited. First, nearly all ongoing behavioral genetic studies rely on large, population-based samples. As such, they would provide ideal vehicles for introducing specific indicators of macrocontextual features that may affect the role that genes play in pathways to nicotine dependence. Second, behavioral genetic designs are by definition family based. This provides enormous opportunities to expand the focus on microcontextual influences that either operate as family process or impinge on family members such as twins and siblings (e.g., peer groups). Although the range of both macro- and microcontextual factors that could be included in genetic

studies is wide-reaching, the focus here is on *illustrative examples* using specific constructs that have been linked with smoking, can be folded with relative ease into ongoing genetically informative designs, and, perhaps most important, can be pursued with measurement strategies that attempt to move from the distal to the more proximal level.

Socioeconomic Status: Moving from Distal to Proximal Influence

The few behavioral genetic studies of smoking or substance use that have attended to macrocontextual factors suggest that more detailed quantification of the social environment is warranted. This section illustrates the potential for genetic studies of smoking by highlighting one (of many) prominent aspects of the social environment with strong relevance for smoking in both adolescents and adults: socioeconomic status (SES). A number of studies provide good examples of links between SES and smoking in a wide range of populations. SES effects on smoking are not limited to adolescent smoking and continue into early adulthood.[33] Indeed, the effects of SES have been observed at all stages of smoking—from initiation in adolescence through progression to regular smoking and smoking persistence in adulthood—as linked by continuities between childhood (parental) SES and adult (individual) SES.[34,35] In addition, changes in educational attainment in young adulthood alter the trajectories of smoking. For example, although adolescent smoking strongly predicts smoking in adulthood, an improvement in SES (moving to a higher SES level in adulthood as compared to childhood SES) reduces the likelihood of progressing to persistent smoking in adulthood.[36] Although SES effects may operate through multiple levels of influence, including linkages with parental smoking and parental behavior, direct links between parental education level and offspring adult smoking have been found after controlling for these factors.[37]

It is worth noting that at this point incorporation of SES—even measured as a distal environmental construct—into behavioral genetic designs would be a step forward for the field. The modeling approach that has been used in prior behavioral genetic studies to test for cohort and cultural variations in the etiological architecture of smoking would be well-suited to test for evidence of gene-environment interplay with SES as a measured contextual variable. For example, SES has been shown to moderate the heritability of IQ[38] and cognitive aptitude;[39] in both cases, shared environmental influences are pronounced in impoverished families but genetic effects predominate in affluent families. Given the wealth of studies linking both childhood and adulthood SES to all stages of smoking, the dearth of behavioral genetic studies that have explored SES as a potential moderator of the etiological architecture could easily be rectified, especially given that there are solid conceptual models that provide a rationale for examining such effects.[6]

Nuanced Approaches to Capture Proximal SES Effects

Consistent with the theme of this section, there are nuances to the measurement of SES that would be instructive for genetically informative studies. For example, Unger and colleagues[40] have shown that two features of SES—an objective SES index (based on a composite measure of family and neighborhood SES) and available pocket money—are associated with an increased risk of smoking in a sample of 8th-grade adolescents. This study is interesting in that attention was given to both a more proximal indicator in the adolescents (their own available spending money) as well as a specific effect of neighborhood SES (as determined by matching zip codes to U.S. Census data). Both of these steps reflect

progress in moving toward more proximal indicators of the macroenvironment in that there are multiple levels of proximal influence that operate at both the individual level and the neighborhood or area level (again, see chapter 3 for a similar perspective on measurement of phenotypes). Diez Roux and colleagues[41] used more detailed information available from census data, including census tracks (subdivisions of a county), as well as smaller components (or blocks), to measure a number of area characteristics. Such measurement of socioeconomic disadvantage was highly predictive of smoking in young adulthood in their study, and as suggested in this paper, individual- and area-level indicators of SES may capture unique aspects of socioeconomic effects. Also, evidence shows that area-defined economic deprivation is predictive of the likelihood of quitting smoking.[42] These studies provide important examples of obtaining more precision on macrosocial factors, and clearly a variety of other variables—such as cigarette prices and presence of smoking restrictions—that are geographically linked deserve consideration in future studies.

Proximal Indicators of Area Effects on Smoking

The studies above highlight the early steps that are being taken to break down the distal factor of SES into a number of components, with the net result being more specific indicators of the macrocontext that may likely alter the mix of genetic and nongenetic influences on smoking during both adolescence and adulthood. The overriding implication for genetic studies of tobacco use and nicotine dependence is that there are not only crucial macrocontextual influences that shape patterns of smoking (and undoubtedly intersect with genetic susceptibility) but also *specific methodologies* that permit more precise assessment of these factors at a proximal level. A number of emerging constructs and measurement techniques could be relevant as predictors of smoking, including a focus on area crime rates,[43] neighborhood disorder,[44] price of cigarettes, and presence of a smoke-free law. One illustrative example is the density of tobacco retail outlets as a specific area risk factor linked with cigarette smoking, especially in youths. A paper by Novak and colleagues[45] illustrates the conceptual basis as well as a highly detailed methodology as applied in the Project on Human Development in Chicago Neighborhoods. In this study, trained raters videotaped, while driving, each side of streets that corresponded to selected census tracks. Codes were developed to identify retail locations licensed to sell tobacco and captured empirically as density of retail outlets. Two findings of the study are especially relevant: (1) retail tobacco outlets were overrepresented in socially and economically disadvantaged neighborhoods (suggesting a more proximal level of risk for smoking via area SES), and (2) youths who resided in the high-density areas were at increased risk for smoking, especially after controlling for confounding variables.

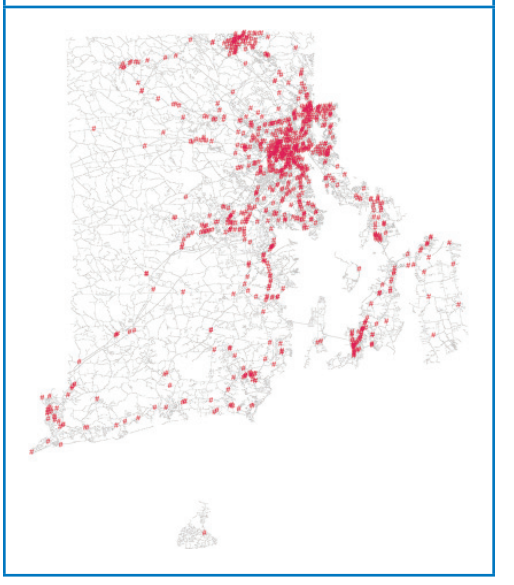
It is unlikely that large-scale behavioral or molecular genetic studies would invest the resources to physically code diverse geographic areas for density of retail tobacco outlets. The advancement in methodologies such as geographic information systems (GISs) provides a cost-effective approach for capturing such specific social contextual factors with relevance for smoking. Croner and colleagues provide an informative and readable description of the methods and utility of GISs, which they describe as computer-based programs "supporting the collection, storage, retrieval and statistical manipulation of spatially-referenced observations and events."[46(p1961)] Fundamentally, any study that collects street address data on participants has the capacity to extract information from sources such as census data (as discussed above in studies of area effects on smoking), as well

as geocode or address match to spatial data (i.e., map coordinates), and utilize any number of indicators for features of interest from relevant databases.

To demonstrate the utility of this approach, this chapter briefly describes portions of ongoing work at the Brown University Transdisciplinary Tobacco Use Research Center (Brown TTURC) as applied to the third (adolescent) generation of its three-generation family study of nicotine dependence. The study was successful in using GISs to match density of tobacco retail outlets that correspond to the locations of participants. The geocoding process required three types of files: TIGER/Line, census block groups, and address tables. *TIGER/Line* is the term given to files containing the layout of U.S. streets, and *census block groups* is the term given to the files containing the layout of the U.S. Census block groups, which, at the time of these analyses, were the smallest geographic unit of measurement of the U.S. Census. Lastly, tables containing physical addresses of participants and cigarette retailers were needed that contained U.S. street addresses and zip codes. The addresses of cigarette retailers for Rhode Island and Massachusetts (the two primary states of residence for participating families) were obtained electronically from the Rhode Island Division of Taxation and the Massachusetts Disclosure Office. Figures 11.1 and 11.2 present the located cigarette vendors within each state as spatial points on a map of the state.

A number of variables can be generated from these data, including counts of cigarette vendors per census block group per state and the density of cigarette vendors within specified distances of each participant. For example, one measure can be created to index if there is any outlet in the given area, and another can be based on the proportion of block faces with a given outlet. Physical distance and traveling time to the closest

Figure 11.1 Located Cigarette Vendors in Rhode Island

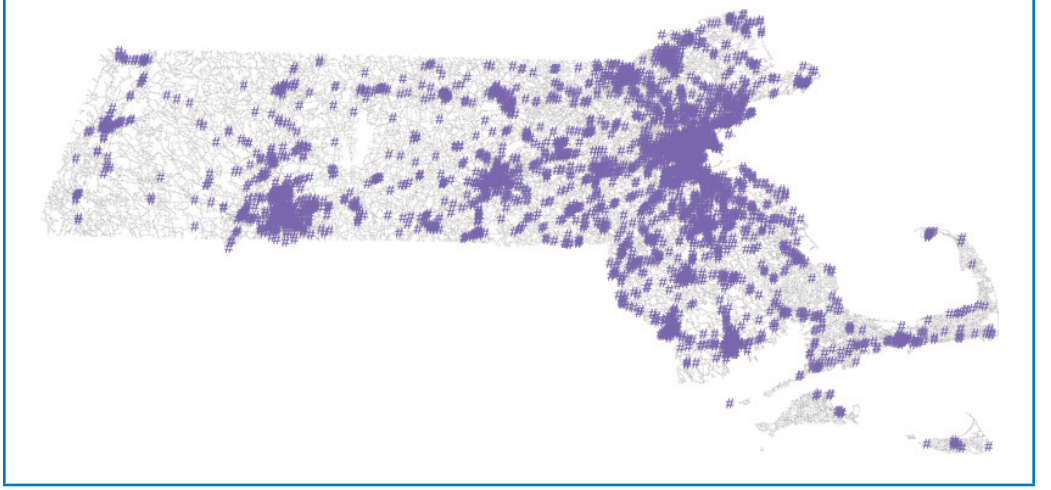


and the second-closest tobacco and alcohol stores can also be calculated by using network analysis in GISs.

Implications for Incorporating Proximal Indicators of the Macroenvironment in Genetically Informative Studies

Four basic points can be extracted from these examples of methods that can be used to move to a more precise and "molecular" level of understanding the macrocontext within genetically informative studies. First, genetic and family-based studies provide an excellent platform for applying relatively new methodologies such as GISs, as well as many other approaches now used to generate sophisticated indices of macrocontextual influences with empirically demonstrated relevance for smoking. Second, integrating these approaches into genetically informative designs will be most effectively accomplished via a transdisciplinary framework,[1] which facilitates collaboration across a number

Figure 11.2 Located Cigarette Vendors in Massachusetts



of disciplines. Third, these proximal constructs that can emerge from methods such as GISs can be as easily integrated into quantitative genetic models as any distal measure, such as SES as traditionally represented, and would provide needed data on the extent to which expression of genetic liability to multiple indices of smoking (initiation, persistence, dependence) is modified by macrocontextual factors. Finally, proximal indicators of the macrocontext could also serve as putative environmental components in a variety of models of gene-environment interplay (e.g., gene-environment interaction and correlation)[5,6] when combined with measurement of candidate gene markers with relevance to nicotine dependence.

Quantifying the Microsocial Context: Moving Toward Proximal Measures of Interpersonal Influences on Smoking

As was the case for the macrocontext, a multitude of microcontextual factors could impinge on likelihood of smoking across developmental stages. Building upon the behavioral genetic studies reviewed earlier that incorporated interpersonal influences into estimates of the etiological architecture of smoking, this section focuses on methods that attempt to yield more proximal indicators of potential underlying social processes. This focus not only reflects an important theme in the behavioral genetics of smoking, but also provides a logical extension of genetically informative designs, given the inherent attention to dyadic relationships (e.g., twins and siblings; parents and offspring).

Interpersonal Relationships as a Context for Smoking

Independently of the behavioral genetic literature, tremendous attention has been given to interpersonal relationships as social contexts for the development of multiple forms of substance use,[47] including smoking.[10,48,49] Indeed, some perspectives emphasize the critical importance of social networks as an influence on smoking,[32] which have been conceptualized as being comparable to an "infectious disease" model[50] or "social contagion."[29] Particular focus has been placed on three types of relationships as

the most salient for smoking: parents, peers, and siblings. There is a long history of studying parental smoking as a predictor of offspring smoking.[51] A number of studies have provided further evidence of linkages between parental smoking and a number of smoking outcomes in adolescence and adulthood. Parental smoking increases the likelihood of experimentation in childhood and adolescence[52] and regular smoking in early adulthood;[53] smoking parents who provide a smoke-free home for their children may confer particular protection against smoking initiation.[54] Adolescent offspring of mothers who smoke regularly and/or are nicotine dependent are more likely to initiate smoking and to progress to nicotine dependence.[55] Parental smoking, including paternal smoking, also predicts an earlier age of onset of tobacco use.[56] A number of studies also suggest that parental smoking cessation is associated with a decreased risk of smoking in adolescent offspring.[57–60] These studies all go to the broader point that social networks (and the resultant proximal effects of social influence) may have a profound effect on patterns of smoking.[31,32]

A similarly large historical literature exists for peer influences on adolescent cigarette smoking, whereas less attention has been given to siblings. Reviews by Hoffman and colleagues and Kobus describe multiple theories of peer influences and provide a comprehensive longitudinal model.[49,61] Hoffman and colleagues[61] provide a good discussion on the core concepts of peer influence (as a putative causative factor) and peer selection as they pertain to smoking.[62] The impact of sibling smoking has begun to receive more attention, especially given the strength of the association between siblings,[29,51] and the overviews of the models of sibling influence provided by Slomkowski and colleagues.[30] Subsequent studies have confirmed the strong predictive value of friend and sibling influences on adolescent smoking.[63–65]

Proximal Indicators of Interpersonal Influence

The extensive data on interpersonal relationships as a social context for the development of smoking suggests that incorporation of social processes into genetic models would be profitable and perhaps necessary and is consonant with an emphasis in the literature on the effects of social networks and influences on smoking.[31,32] As stated earlier, the behavioral genetic literature consistently points to shared environmental effects on smoking in adolescence; one source of influence could be joint social relationships and direct influence of smoking behavior within intimate relationships. As reviewed earlier, some progress has been made in behavioral genetic studies suggesting that, as a structural variable, both having friends who smoke and having a parent who smokes moderate the shared environmental effect on adolescent smoking. Furthermore, prior studies[29,30] that focused on specific dimensions of the sibling relationship as moderators of shared environment have inched toward more specific indicators of social process. However, little attention has been paid to translating the typically measured distal factors of having a relationship with someone who smokes into more proximal measures of social influence that can be studied within the gene-environment interplay framework. This section illustrates an approach for incorporating proximal indicators of interpersonal influence into genetically informative designs. Although the focus here is on interpersonal dynamics, the broader point is the need to appropriately consider and measure a host of powerful social contextual factors into genetic studies, including influences such as exposure to cigarette advertising and smoking in movies,[66] which may operate via social networks such as peers.[67]

Two rationales based on the empirical work available support the relevance for

genetic models of nicotine dependence. First, the consistent isolation of sources of shared environment in studies of adolescent smoking, some of which may be embedded in interpersonal dynamics,[26] could identify candidate "environmental" factors to study jointly with both latent genetic indicators as well as candidate gene markers for propensity for nicotine dependence within the gene-environment interaction framework.[4,5] Second, given evidence that components of family and peer relationships may reflect genetic as well as social influences,[68] it would be informative to explore the possibility of gene-environment correlation as one source of the net genetic effect on smoking and nicotine dependence. In addition to filling in the black box of heritability, such work could contribute to identifying multiple sources of genetic influence on smoking. For example, Agrawal and colleagues[53] suggest that correction for a host of risk factors, including parental smoking and features of the parent-child relationship and home environment, yields a reduction in the overall heritability of regular smoking in young adulthood that nonetheless remains significant. They draw two important conclusions from these results: (1) the reduction in heritability may signal that part of the overall parental effect reflects genetic effects, and (2) the residual heritability of young adult regular smoking may represent more "phenotype-specific" genetic effects.

Proximal Indicators of Social Influence: Methods for Studying Real-Time Interaction

The most traction will be made in developing gene-environment models focusing on social context relationships by using specialized methodologies capable of capturing more proximal indicators of interpersonal processes that are linked with risk for smoking and progression of smoking.[47] A number of processes could be studied. For example, selected parental behaviors could be measured and inserted into behavioral and molecular genetic studies, including parental beliefs and behaviors pertaining to smoking,[69] parenting style and smoking-specific parenting practices,[70] and antismoking socialization.[71] Another example with respect to peers would be social network analysis, which, as described by Hoffman and colleagues,[61] can be used in longitudinal studies to tease apart peer influence and peer selection. Other interesting methods include using speech samples to extract relationship narratives as an indicator of mother-child family process[72] and sibling-expressed emotion.[73]

Similar to the strategy of focusing in some detail on GIS methods in the prior section, this section will provide an illustrative example that has been used especially in studies of both peers and siblings: the use of microsocial coding of real-time social interaction as captured by using semistructured, videotaped paradigms. One paradigm that elicits and records relationship dynamics is to observe microsocial interaction as it unfolds in real time.[74] Typically, semistructured discussion tasks are constructed and videotaped without an observer present. Dishion and colleagues have pioneered this work with particular reference to microsocial processes that convey risk for antisocial behavior and substance use,[75,76] and similar work has been done with siblings.[77]

Real-Time Social Interaction in a Genetically Informative Design

Two features of this methodology warrant expansion in terms of immediate relevance to the etiological architecture of smoking as it changes from adolescence to adulthood. First, the genetically informative Nonshared Environment in Adolescent Development (NEAD) Project, which uses monozygotic and dizygotic twins along with full, half, and unrelated sibling pairs, has provided a wealth of data on the

genetic and environmental determinants of sibling behavior in adolescence via the combined use of videotaped interaction and multirater reports.[78] A key finding is that a number of indices of sibling relationship dynamics are shaped by shared environmental, rather than genetic, factors as determined by biometrical model fitting. Given the accumulating evidence, reviewed earlier, that shared environmental factors influence adolescent smoking and that sibling interaction may moderate, in part, the shared environmental effect, the elucidation of specific interpersonal processes derived from microsocial data would provide a strong candidate for this form of proximal environmental influence on smoking. As discussed in the examples for macrocontextual factors, such empirically validated indicators of environmental influence would serve well in gene-environment interaction models of adolescent smoking that are optimally tested by using proximal measured environmental pathogens.[4,5]

A second theme from the NEAD Project is that shared environmental influences provide the most robust linkage across different types of relationships, including covariation between mother-adolescent and sibling relationships as well as longitudinal associations between adolescent antisocial behavior and young adult relationships with romantic partners.[78] These findings are included for consideration as part of the thesis that the interpersonal dynamics that may underlie both peer and sibling influences on smoking in adolescence may represent enduring relationship styles that carry into adulthood and into other relationships, including relationships with romantic partners. These patterns may be especially relevant given the notable evidence for assortative mating for a number of stages of cigarette smoking that include regular smoking and nicotine dependence.[79,80] Although assortative mating may primarily reflect selection rather then interpersonal influence per se, it is worth considering the possibility that the continual construction of intimate relationships may be influential in maintaining lifestyle choices across developmental periods that promote harmful behaviors.[81] It is worth reiterating at this point that current contact between adult twins is associated with twin resemblance of nicotine dependence.[23] The proposed utility of microcontextual measures of proximal, interpersonal influences may not only be useful as a piece of the etiological architecture of adolescent smoking but also could be expanded to include adult relationships as a putative source of environmental reinforcement for smoking; this could, in principle, interact with emerging genetic propensity for nicotine dependence. The application of these methods would provide the most sensitive tests for the role of interpersonal influences in models of nicotine dependence that posit the possibility of gene-environment interplay.

Ecological Momentary Assessment

A final, newer methodology available to the smoking field is ecological momentary assessment (EMA). Indeed, the rationale for EMA is now well recognized in the smoking literature and has been well explicated.[82,83] The "ecological" aspect refers to the use of technologies—for example, personal digital assistants (PDAs) and cellular phones—that allow respondents to report their behaviors in real time and in real-life settings. The corresponding "momentary assessment" of the methodology is the emphasis on acquiring instantaneous self-reports to minimize the recall bias and memory distortion typically introduced by more retrospective accounts.

EMA Studies of Smoking

A number of published studies have used EMA to assess smoking behavior in

adolescents and adults. EMA has been used to examine differential smoking patterns in adult heavy smokers and chippers.[84] Some of these studies have assessed antecedents of cigarette smoking in adults, especially a variety of affective states,[85,86] as well as prospective indicators of smoking lapses,[87–89] which have implications for knowledge about the smoking relapse process.[90] EMA methods have been used successfully with adolescents as well; these methods have shown links between tobacco use and both high levels of anxiety[91] and symptoms of attention deficit hyperactivity disorder.[92]

The interest here in bringing attention to the EMA methodology is twofold: it holds great promise for merging the microcontext, such as interpersonal interactions, with internal states and cognitions, and it permits a simultaneous level of measurement of macrocontextual features. The essence of the approach is being able to repeatedly prompt participants in "real-time" and "real-life" contexts with questions concerning how they are feeling, what they are doing, who they are with, and where they are. For example, Shapiro and colleagues[93] reported that adult smoking was associated with particular activities and locations such as work breaks, being in a car, and outdoors, reflecting the increasing restrictions on where smoking can take place. Chandra and colleagues[94] have found that environmental restrictions seem to affect the smoking patterns of some individuals more than others.

The interesting studies reviewed above begin to highlight the potential for using EMA to assess, in an integrated and ecologically sensitive manner, actual smoking behaviors along with concurrent information on affective and cognitive states, interpersonal contexts, and broader macrocontexts (and although not reviewed here, it is also possible to record physiological data as well by using ambulatory recording methods) within genetically informative samples. The intensive, repeated intervals that can be used during the day and across days permits a complex stream of potential antecedents, correlates, and consequences of smoking which, when crossed with a genetically informative design, will yield a potentially overwhelming overlay of proximal variables at multiple levels of analysis. Sophisticated data analytic tools have been (and continue to be) developed to work with such "intensive longitudinal data."[95]

Illustration of EMA in a Family-Based Design

To demonstrate the feasibility of collecting EMA data in a family-based design, this section contains a brief overview of methods and some illustrative data derived from the ongoing Sibling Partners Study. This study focused on 60 adolescent sibling pairs drawn from the New England Family Study who have participated in the three-generation family study of nicotine dependence by the Brown TTURC. The sibling pairs were recorded in real time, using programmed PDAs, with a variable interval between their prompts to minimize subject reactivity while permitting logical overlap in the chronology of their responses. They were prompted on a variable schedule every 30 to 45 minutes, starting with the time they typically woke and ending with the time they typically went to sleep (these times were determined for each projected day of recording during an intake interview conducted the night before data collection began). Participants were also allowed to indicate times during the day when they structurally could not respond to the prompts (e.g., sports practice) and were also instructed not to respond to the PDA if that behavior could be harmful (e.g., while driving). Because this was a family-based design with participants from multiple states, data were recorded during school hours. Participants were asked to provide daily responses to the PDA for six consecutive days; the same protocol was used both 6 months and 12 months after the baseline assessment.

This study illustrates a few aspects of the methodology that may be useful for future genetically informative designs (such as twin studies). First, the compliance rate (at each wave and across waves) was excellent. Nearly all subjects responded to over 80% of the PDA prompts (producing on average more than 100 data points across the six days of recording at each wave). Second, table 11.1 provides examples of some of the PDA diary items along with response choices to demonstrate how social context, mood, interpersonal dynamics, and smoking behaviors can be assessed (it takes approximately 60 seconds for a participant to respond to all 47 prompts).

Third, preliminary descriptive data are presented to show how smoking behavior, recorded every 30 to 45 minutes, varies according to two levels of social context as represented by two diary items: "Location" (Where Am I Now?) and "Whom" (Right Now, I Am With). Graphs (see figure 11.3) show the percentage of diary responses to each "Cigarettes" prompt (Since Last Beep # of Cigarettes Smoked) aggregated over the six-day recording period across all individuals; note that these data are presented descriptively, without application of the statistical models suitable to these data, to simply show the potential utility of EMA.

For these purposes, the responses were dichotomized, and the figures show the percentage of epochs in which any cigarette smoking was endorsed (as opposed to "none at all") as a function of both "Location" and "Whom." The number of epochs with a positive endorsement of any smoking was higher when with the sibling partner as compared with when alone, with other family members, or with other family members plus the sibling partner. There are also suggestions that "Location" plays a role; for example, smoking percentages with a sibling increase when at a shopping mall but decrease at this location when with other family members (with or without the sibling partner). Again, these percentages demonstrate how multiple levels of both micro- and macrocontext can be combined using EMA. To illustrate this further, figure 11.4 summarizes the pattern of endorsed smoking epochs over the six-day period for a concordant pair of siblings who are often concordant at real points in time. For each data point represented, information on where they were, whom they were with, their moods, and dynamics of their interactions with each other are included.

Potential Contribution of EMA to Genetically Informative Designs

In summary, newer methodologies such as EMA offer untapped potential for genetically informative designs from the perspective of exploring gene-environment interplay because of the unique opportunities to gather simultaneous, ecologically valid, proximal indicators of social context. Application to twin studies (and similar genetic designs) would allow a new class of questions to be asked on the degree to which smoking behavior varies as a function of both genetic similarity and social context. Furthermore, EMA methods could be used to examine or validate differential smoking patterns in individuals as a function of both candidate gene markers and proximal indicators of social context. Finally, given the perspective that smoking phenotypes will involve multiple levels (chapter 3), the simultaneous assessment of smoking behavior along with both micro- and macrocontextual information could eventually yield novel phenotypes for genetic studies that are defined, in part, by the context in which they arise.

Future Directions

The findings presented in this chapter have two key implications. First, it is possible that overall population estimates of the heritability of smoking could reflect an aggregation of very different etiological

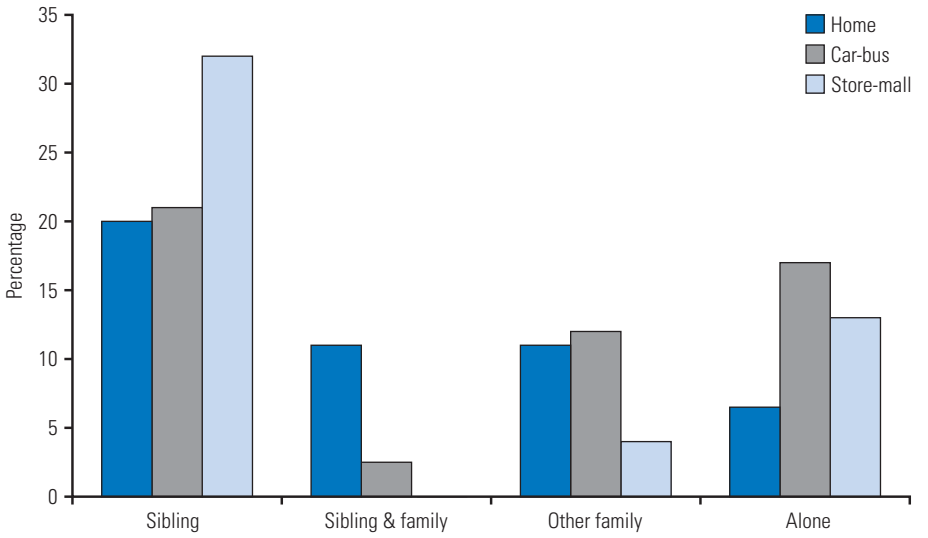
Table 11.1 Sibling Partners Diary Prompts

Location	Where am I now? Home Friend's School or work Store or mall Event Car-bus Outdoors Somewhere else
Whom	Right now, I am with: Sib-partner Other family Both Neither
Activity 1	What am I doing now (primary activity)? Getting ready Homework Computer TV or music Hanging out w/ friends More choices
Activity 2	What am I doing now (primary activity)? Exercise/sports Errands/chores Hanging out Talking/phone Videos or games Other activity Go back
Activity_with 1	I am doing this: Alone With someone
Activity_with 2	Who am I doing this with? (check all) Sib-partner Other siblings Mother Father Other adults Friends/others
Activity_with 3	Who (else) is nearby? (check all) No one Parents Other siblings Friend(s) Other adult(s)
Irritated	How irritated/angry am I feeling now? Not at all Just a little Pretty much Very much
Relaxed	How relaxed am I feeling now? Not at all Just a little Pretty much Very much

Table 11.1 Sibling Partners Diary Prompts *(continued)*

Focused	How focused am I feeling now? Not at all Just a little Pretty much Very much
Worried	How worried am I feeling now? Not at all Just a little Pretty much Very much
Sib_with	Been w/ your sib-partner in the last 45 minutes? Yes No
Sib_quality	Quality of my interaction w/ sib-partner was (check all): Special Pleasant Neutral Uncomfortable Confrontational No interaction in last 45 min
Sib_annoyed	In the last 45 min I'm a bit annoyed at my sib-partner My sib-partner is a bit annoyed at me Both are true Neither is true
Sib_talked	In the last 45 min my sib-partner & I talked Not at all Just a little Pretty much Very much
Sib_feel_good	While together he/she made me feel good about myself? Not at all Just a little Pretty much Very much
Sib_argued	While together we argued/fought Not at all Just a little Pretty much Very much
Sib_mischief	What we did together might be considered mischievous Not at all Just a little Pretty much Very much
Urge_smoke	In the last 45 min my urge to smoke: Not at all Just a little Pretty much Very much
Cigarettes	Since last beep # of cigarettes smoked: A few puffs 1 to 2 3 to 5 More than 5 None at all

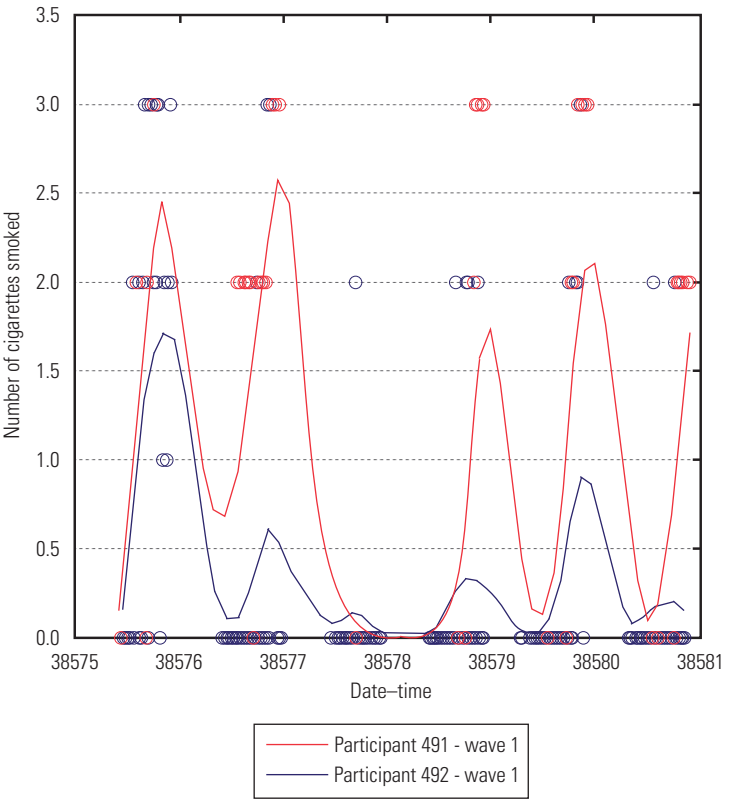
Figure 11.3 Percentage of Diary Responses Endorsing Cigarette Use Stratified by Social Contexts



architectures that vary on the basis of measurable social contextual factors. Thus, there may be etiological heterogeneity in the mix of genes and environments that can only be captured by incorporating candidate social contextual measures in genetically informative designs. *Insight into the mechanisms underlying such etiological heterogeneity will not be achieved without considering a broad number of both macro- and microsocial factors.* Although this chapter focused on highly selected social contextual factors to illustrate a number of concepts and methods of relevance to genetically informative designs, the analogy can be made that a "whole-environment" scan would carry as much importance as a whole-genome analysis in the eventual construction of satisfactory mechanistic etiological models of nicotine dependence. Second, evaluating sources of etiological heterogeneity may help in understanding the mechanisms by which endophenotypes (chapter 8) become salient for smoking behaviors under specific environmental conditions and not others. That is, crossing advanced measurement of both endophenotypes and social contexts may illuminate core environmental factors that dwarf individual-level propensities as well as highlight especially prominent endophenotypes that convey risk under particular environmental conditions.

It is reasonable to assume that a multitude of genetic strategies eventually will yield replicable findings supporting multiple genes with direct relevance to nicotine dependence, such as the 2007 report from Bierut and colleagues.[96] It also is reasonable to postulate some direct pathways between candidate genes and propensity to develop nicotine dependence that may be somewhat impervious to the social environment, once exposure to nicotine takes place. However, it is becoming increasingly untenable to ignore social contextual factors without sacrificing a broader and more comprehensive understanding of the etiological architecture of complex phenotypes such as nicotine dependence. Furthermore, taking the perspective that nicotine dependence is an end point of

Figure 11.4 Pattern of Endorsed Smoking Epochs over a Six-Day Period for a Concordant Sibling Pair



complex behavioral and physiological pathways that stretch across multiple periods of the life course reinforces the notion that empirically supported environmental influences on earlier stages of smoking play, at a minimum, an indirect role in shaping the expression of genetic susceptibility.

If the field is to take seriously the proposition that gene-environment interplay will play a key role in eventually understanding the mechanisms by which genes contribute to smoking behavior and nicotine dependence,[1] a dedicated effort will be needed not only to incorporate environmental measures with more regularity and vigor but also to invest the time, resources, and collaborative expertise necessary to provide the best available data on the environment.[4,5] It is worth noting here the Genes, Environment and Health Initiative of the National Institutes of Health,[97] which includes a component to develop novel and precise measures of exposure to disease-causing agents in the environment.

Summary

The key yield from behavioral genetic studies of smoking that have included attention to the social context is that they demonstrate how the heritability of complex phenotypes can fluctuate, depending on varying social factors. Genetic pathways to nicotine dependence are not activated if social

conditions dampen the likelihood of smoking initiation (as is the case for females in China) as would be predicted by application of the genetic epidemiological triangle to smoking. Certain socioregional characteristics can either diminish the impact of heritable influences on substance use or make genetic differences across individuals salient (as is the case for adolescents in Finland). Some of the predictive power attributed to genes in quantitative genetic models may be explained away by microsocial influences such as having peers, parents, and siblings who smoke (as is the case for adolescents in the Netherlands). These studies provide empirical evidence that the extent to which genetic differences between individuals affect the likelihood of smoking depends in part on multiple levels of the social context, reinforcing that genetic effects for complex phenotypes are not deterministic, but rather probabilistic, and best defined via reference to the social environments in which they arise.

This chapter has provided a highly selective overview of relatively new methods for assessing "molecular" aspects of social context at both a macro and micro level. These methods were chosen to illustrate approaches that make conceptual sense in typical behavioral genetic or epidemiological designs and that can fold into these designs with relative ease, given both the types of samples studied and the size of such samples. Although there are costs involved in the application of these methods, these need to be weighed against the likelihood of their necessity in building more comprehensive and realistic models of genetic effects on smoking.

Conclusions

1. Social context influences on developmental pathways to nicotine dependence reflect gene-environment interplay that comprises the elements of a traditional epidemiological framework including a host (e.g., smokers and genetic endowment), environmental factors (social network), and an agent (e.g., tobacco).
2. Macrocontextual factors such as culture, socioregional variables, and socioeconomic status can modify or even nullify genetic influences on nicotine dependence. For example, a twin study revealed a prevalence rate for smoking of less than 1% in Chinese women, reflecting an inhibitory cultural influence. Family or neighborhood socioeconomic status and density of tobacco sales outlets are examples of specific contextual factors that appear to influence smoking risk among adolescents.
3. Microcontextual approaches have revealed factors such as exposure to parental, sibling, and peer smoking that may moderate genetic influence on behavioral smoking measures. The genetically informative Nonshared Environment in Adolescent Development Project, which comprised twins as well as other siblings, indicated that sibling interaction patterns may moderate the shared environmental effects that influence adolescent smoking.
4. Studies of smoking behavior using ecological momentary assessment, designed to measure both macro- and microcontextual factors, show that smoking behavior varies with both location and companions. Such assessments serve as a possible future model for incorporating integrated social context issues such as actual clinical and public health efforts to reduce tobacco use within etiological architectures.
5. Future work incorporating social context within gene-environment studies of smoking behavior and nicotine dependence will benefit from a greater focus on environmental factors, including more-fine-grained and comprehensive assessments of potential environmental influences.

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