

---

# Index

## A

- $\alpha 4\beta 2$  nAChRs, 166, 168
- $\alpha 7$  nAChR receptors, 168
- $\alpha 7$  nAChR subunit knockout mice, 159
- abstainers (nonsmokers)
  - characteristics of, 22
  - inclusion *versus* exclusion of, 222–223, 235, 323
  - nicotine patches, 377
- abstinence
  - in behavioral economics effects, 420
  - deficits, 350–351
  - effects of, 405, 408
  - event-related potential, 429
- abstinence-induced craving, 438
  - effects of, 405
  - measurements, 403
  - during smoking cessation, 441
- $\alpha$ -bungarotoxin binding, 165, 167
- ACE model, 249–250
- acetaldehyde (alcohol studies), 86–87
- acoustic startle reflex. *See* startle response
- active avoidance, 435
- acute stress mimicry of withdrawal symptoms, 448
- acute tolerance, 162–163
- ADA (Americans with Disabilities Act), 49
- Add Health (National Longitudinal Study of Adolescent Health), 197–198, 261, 517
- addiction. *See also* nicotine dependence;  
substance use
  - clinical manifestations of, 79
  - as dependence, 77
  - DRD2* gene and, 32
  - versus* habituation, 24
  - models of, 293
  - versus* smoking, 24
  - stress and, 36
- additive components, 511
- adenosine knockout mice, 159
- adenosine systems, in nicotine reinforcement, 159–160
- ADHI\*2* alleles (alcohol studies), 86–87
- ADHD. *See* attention deficit hyperactivity disorder
- adipose tissue, nicotine concentrations in, 145
- ad libitum (ad lib) self-administration, 415–416, 419
- administration, 145–149, 418. *See also* self-administration
  - in drinking water, 148, 172
  - intravenous, 146, 156, 410
  - oral, 148, 154, 412
- adolescent(s)
  - alcohol use by, 516
  - cognitive control, 358, 380
  - delay discounting choices, 350
  - depression in, 351–352
  - event-related potential, 429
  - extraversion in, 349
  - first mood effects, 375–376
  - neuroticism in, 351, 352
  - nicotine deprivation learning deficits, 436
  - nicotine response in, 194–195
  - novelty seeking behavior, 27, 348
  - P300 amplitude in, 360
  - physiological changes in, 589
  - protective factors, 343
  - research limitations, 367
  - social influences on, 346–347, 517
  - substance-use vulnerability of, 195, 199, 200–201, 212, 233–234, 261, 292–293
  - transition to adulthood, 195
  - use of genetic information by, 46–47
- adolescent developmental trajectories, 189–235, 592
  - age of smoking onset, 200–201
  - empirically identified, 202–214
  - example of, 223–233
  - future research directions, 233–234
  - psychopathology, 191–202, 292–293
  - statistical models, 214–223
  - substance use, 295–296 (*See also* substance-use comorbidity; *specific substance*)
- adolescent nicotine dependence, 191–195
  - animal models of, 155, 194–195
  - biological vulnerability for, 100, 193–195, 200–201, 233
  - future research directions, 233
  - genetic studies of, 86, 264–266, 342
  - individual symptoms of, 192
  - measurement of, 192, 230–231, 264
  - time and exposure required for, 192–193
  - withdrawal symptoms, 192
- adolescent smoking, 371
  - antisocial behavior and, 200, 202, 211, 232
  - environmental influences on, 196–197
  - ethnic differences in, 213–214, 279

- gender differences in, 196, 199, 260, 263–264, 342
  - gene-environment interactions in, 197–200, 259
  - genetic research on, 195–200, 259–269
  - heterogeneity in, 190, 233
  - as indicator of adult nicotine dependence, 230–231
  - latency between cigarettes, 371
  - molecular genetic studies of, 198–199
  - parental smoking and, 196–197, 200
  - peer smoking and, 197
  - prevalence of, 191
  - twin studies of, 196, 259–262
- adolescent smoking initiation, 191
- age range in, 261–262
  - heterogeneity of, 196, 201–202, 233
  - progression to dependence, 341
    - genetic studies of, 263–264
    - rate of acceleration, 201–202
  - psychosocial factors, 200, 202, 211
  - risk profile, 211–212, 232
  - shared environmental factors in, 260–261, 264, 280
- adoption studies, 196, 279
- ADRA1A* gene, 42
- adulthood, transition to, 195
- adult nicotine dependence, adolescent smoking indicators of, 230–231
- adult-onset events, 100
- adult smoking phenotype, limitations of, 190
- advertising
  - costs of, 21
  - in movies, 7, 20, 523
  - novelty seeking as response to, 348
  - protobacco, 7, 20, 30, 348
  - smoking index variable and, 30
- aerosols, nicotine, 147
- affective coping, 112–113
- affective response, 373–376
  - future research directions, 456
  - physiological measures of, 377–378, 445–446
  - regulation of, 358, 403, 443–449
- affiliation/empathy system, 362
- African Americans
  - adolescent smoking in, 213–214
  - genotypes linked to dependence, 47
  - linkage study focused on, 267
- age effects, 170–171
  - factor loadings by, 271–276
  - in smoking initiation assessment, 261–262, 279, 281, 322
  - in substance-use comorbidity, 322–323
- age-gene-environment interactions, 589
- age of onset, 26, 100, 371–372
  - developmental trajectories by, 200–201
- age-related macular degeneration, 46
- age-specific risk, measurement of, 35
- aggregate effects in complex pathways, 541
- aggression, 357
- agonists (activators), 143
- AHe mice, 435
- AIC (Akaike Information Criterion), 274, 312
- A inbred mice, 154, 165, 412, 422
- A/J mice, 435
- A/J×NMRI cross-bred mice, 154, 412
- Akaike Information Criterion (AIC), 274, 312
- alcohol use
  - adolescent, 516
  - in ATBC analysis, 496
  - Edwards's theory of, 82–83
  - Iowa gambling task as predictor, 350
  - nasal spray use correlated with, 373
  - in NHANES III analysis, 502
  - policies influencing, 294–295
  - as secondary reinforcement, 413
  - side effects, 86–87
  - tobacco use concurrent with, 98, 290, 296–298
    - empirical examples of, 307–323, 496, 502
    - health effects of, 290
    - modeling, 299–305
    - nicotine-dependence correlation, 369, 406, 411–412, 420
  - trajectories of, 295
- ALDH2\*2* alleles (alcohol studies), 86–87
- alertness, 361–362
- allele(s)
  - identical by descent (IBD), 257, 258
  - variants of, 554
- allele frequency, 48, 258
- alpha subunits, 153
- Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), 487, 494–497
- alternative reinforcement, 417
- Americans with Disabilities Act (ADA), 49
- amphetamine, 412
- analysis of variance (ANOVA), 215
- analytic methods. *See also specific method*
  - developmental trajectories, 214–223
  - molecular genetic studies, 257–259
  - phenotypic research, 96–103, 113–118

- anger, palliative effects on, 357  
 animal studies. *See also* mouse models; rat models; *specific strain or study*  
     ad lib administration in, 415  
     adolescent nicotine exposure, 194–195, 589  
     affective regulation, 443  
     dependence, 134–135  
     fetal nicotine exposure, 357  
     impulsivity research in, 449–450  
     reward studies, 372–373  
     transfer to, 350  
 ANOVA (analysis of variance), 215  
 antagonists (inhibitors)  
     CB1 receptors, 160  
     for mu opioid receptors, 160  
     muscarinic receptors, 141  
     nicotine as, 143  
     for nicotine dependence, 159  
 anti-inflammatory effects of nicotine, 148–149  
 antinociception, 162  
 antisaccade task, 359  
 antisocial behavior  
     adolescent smoking and, 200, 202, 211, 232  
     substance use and, 292–293, 304  
 antitobacco stimuli, 20  
 anxiety  
     adolescent smoking and, 201  
     nicotine linkage with, 352–353, 445  
 anxiogenic effects of nicotine, 168  
 apolipoprotein E testing, 48  
 approach, *versus* impulsivity, 378–379  
 approach-related risk, 339, 346–349, 362  
 arousal, 378  
*ASN40ASP* polymorphism, 407  
 aspartame, 412  
 association analysis, 258–259, 268–269, 280  
 assortative mating, 251, 259, 280  
 ATBC (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study), 487, 494–497  
 ATR (Australian Twin Registry), 197, 260–261, 267  
 attention, 361, 378, 432–434  
 attentional bias, 440, 456  
 attention deficit hyperactivity disorder (ADHD), 354–357  
     adolescent smoking and, 201, 211  
     as risk factor, 350, 433  
     substance use and, 292–293, 304  
 attrition biases, 224  
 Australian Twin Registry (ATR), 197, 260–261, 267  
 Automaticity subscale, 90–91  
 aversive mood symptoms, 443  
 avoidance-related risk, 339, 351–354, 362
- B**
- backcrossed mice, 151  
 bacterial contamination, during administration, 145  
 BALB/cBy mice, 164–165, 430–431, 435  
 Barratt Impulsivity Scale, 450  
 Bayes factors, 552, 570  
 Bayesian analysis, 548–549, 570, 572  
 Bayesian False Discovery Probability (BFDP), 573  
 Bayesian Information Criterion (BIC), 310, 312  
 Bayesian model averaging, 117  
 Bayes model, 543  
 BAY K 8644, 167  
 behavior  
     analysis of, 163–164  
     antisocial  
         adolescent smoking and, 200, 202, 211, 232  
         substance use and, 292–293, 304  
     drug-motivated, 404  
     measurements of, 103  
     nicotine and, 151–157  
     phenotypes, 171  
     response systems, 362  
     smoking indices, 80  
     substance-use comorbidity and, 322  
     tolerance, 168  
     traits, 344  
     undercontrol, 98–99  
 behavioral economics, 417, 420, 454  
 behavioral genetics  
     phenotypes in, 492  
     of self-administration, 153–155  
     in social context, 514–518  
 behavioral modeling  
     methodological issues with, 247–248  
     of parental smoking, 246  
 BFDP (Bayesian False Discovery Probability), 573  
 BIC (Bayesian Information Criterion), 310, 312  
 bioavailability of nicotine, 7, 20  
 biochemical indices of smoking, 80, 415  
 biochemical measures of self-administration, 97  
 biochemical pathways, 561  
 BioCyc, 561  
 biological pathways, candidate, 105  
 biological plausibility  
     affective regulation, 443–445

- attention/vigilance, 432–433
  - craving, 438–439
  - event-related potential, 427–428, 429
  - impulsivity, 449–450
  - mood effects, 374
  - reinforcement, 368–369, 410–414
  - resting EEG activity, 425–426
  - rewards, 372–373, 421–423
  - startle response, 430–431
  - working memory, 434–436
  - biological vulnerability, in adolescent nicotine dependence, 194–195
  - biomedical ontologies, 561
  - biometric factor model, 253
  - biometric modeling, 37–45, 86, 88–89, 514
  - BioPAX Ontology, 561
  - bitter taste, 84, 148
  - BKW mice, 443
  - blood pressure, 448–449
  - $\beta$ 2 nAChRs, 153
  - $\beta$ 2 nAChR subunit knockout mice, 159, 166
  - Bonferroni correction, 546, 573
  - brain
    - nicotine concentrations in, 145
    - stimulation, 373
    - upregulation in, 144
    - of young people, 589
  - brain imaging, 360
  - breakpoint
    - drug use, 418
    - nicotine use, 420
    - preferring to wait, 350
  - breast milk, nicotine concentrations in, 145
  - breeding
    - mice, 150–151, 411
    - rats, 411
  - Brown University Transdisciplinary Tobacco Use Research Center (TTURC), 89, 521, 526
  - BUB/Bn mice, 165, 412
  - BUB inbred mice, 154
  - buzz, 374
- C**
- calcium, 136, 139–140
  - calcium calmodulin protein kinase II, 168
  - calcium channel blockers, 162, 167, 168
  - calcium signaling, 167–168
  - Canadian National Longitudinal Survey of Children and Youth, 212
  - cancer genetics, 50
  - candidate biological pathways, 105
  - candidate gene studies, 40–45
    - adolescent smoking, 342
    - discordant phenotype associations, 36
    - epigenetic differences, 37
    - linkage analysis, 32, 40–42, 267–268, 280–281, 589
    - multivariant data, 543–546
    - nicotine dependence, 42
    - prior knowledge of, 559
    - smoking association with, 24
    - SNP relationships over, 545
    - substance-use comorbidity, 325
    - trait pathways, 553
    - variants, 25, 35
  - candidate neural systems, 343–346
  - cannabis. *See* marijuana use
  - Card Arranging Reward Responsivity Objective Test, 350–351
  - CART (cocaine- and amphetamine-regulated transcript), 36
  - cases, in association analysis, 258
  - catechol-*O*-methyl transferase (*COMT*) gene, 269, 408–409, 430
  - categorical covariates, 276–278
  - causal contingent common (CCC) pathway model, 253, 263, 278–279
  - causal differences between groups, 492
  - causal paths
    - phenotypic research, 102, 107–110
    - sensitivity to, 105
    - smoking as, 352
    - types of, 111–113
  - CBA mice, 435
  - CB1 knockout mice, 160, 422
  - C57BL/6 inbred mice
    - conditioned place preference in, 159, 422
    - dose-dependent effects, 165
    - fear conditioning in, 169, 432
    - five choice serial reaction time task in, 433
    - nicotine consumption, 155, 159
    - nicotine-dependence risk, 161
    - nicotine effects in, 435
    - novelty-seeking behavior in, 156
    - oral self-administration in, 412–413
    - prepulse inhibition in, 430–431
    - strain comparisons, 153–154, 164–165
    - in tolerance, 167
  - C57BL/10 mice, 435

- C57BR/cd mice, 435  
 CCC (causal contingent common) pathway model, 253, 263, 278–279  
*CCK* gene, 269  
 CD-1 mice, 443  
 CellDesigner, 561  
 cell signaling, 161, 167–168  
 Center for Antisocial Drug Dependence, 260  
 Centers for Disease Control and Prevention, 498  
 central nervous system (CNS), 344, 348, 353, 354  
 centroid. *See* mean  
 chain smoking, 37  
 children  
     effortful control in, 358  
     secondhand smoke from parental smoking, 246  
     self-control in, 344  
     sleep problems in, 357  
     smoking by, 371  
 children of twins (COT) design, 251–252, 279, 511  
 C3H inbred mice  
     dose-dependence, 165  
     nicotine effects in, 431, 435  
     oral self-administration, 412  
     strain comparisons, 154, 164–165  
     tolerance in, 162  
 chippers (light smokers)  
     adolescent, 213, 232  
     delay discounting, 350  
     genetic factors and, 29  
     *versus* heavy smokers, 43, 81, 83–84, 90, 94  
     prevalence of, 193  
 choice procedure, 369–370, 416, 419–420  
 cholecystokinin (*CCK*) gene, 269  
 Christchurch, New Zealand (CNZ) study, 266  
*CHRNA2* gene, 42, 376–377  
*CHRNA3* gene, 376–377  
*CHRNA4* gene, 268, 407–409, 412  
*CHRNA5* gene, 342, 376–377  
*CHRNA7* gene, 408, 409, 428  
*CHRNA5-A3-B4* haplotypes, 100, 407  
*CHRNA5-CHRNA3-CHRNA4* nicotinic receptor genes, 43  
*CHRNA2* gene, 268, 407, 408, 409  
*CHRNA3* gene, 342  
*CHRNA3-CHRNA6* nicotinic receptor locus, 43  
 chronic exposure, 405, 449  
 chronic smoker endophenotypes, 403, 404–406  
     affective regulation, 443–449  
     cognitive control, 432–438  
     craving, 438–443  
     electrophysiological measures, 425–432  
     future research directions, 452–457  
     impulse control, 449–452  
     investigation rationale, 406–410  
     motivational mechanisms, 410–424  
     summary/conclusions, 457–458  
 chronic tolerance, 163  
 CIDI (Composite International Diagnostic Interview), 81  
 cigarette(s)  
     availability of, 99  
     consumption of, 4, 20  
     design of, 7, 20  
     pricing of, 20, 21, 520  
     vendor locations, 521, 522  
 Cigarette Dependence Scale, 79n  
 Cigarette Evaluation Scale, 423  
 cigarettes per day (CPD)  
     in ATBC analysis, 496  
     with *CYP2A6* gene variants, 418  
     delay discounting correlation, 452  
     as dependence measure, 79, 80  
     in factor analysis, 88–89  
     in NHANES III analysis, 502  
     nicotine metabolism and, 406  
     predictive value of, 80  
     recall reliability, 26–27  
     as smoking cessation predictor, 81, 413  
     in TUS-CPS analysis, 498, 499  
 cigarettes per month, 91  
 class extraction, model misspecification related to, 222  
 classic dependence criteria, 84, 86  
 classification bias, 493  
 class I–IV phenotypes, 28–31  
 class membership, for familial resemblance, 256–257  
 clinical preventive services, 4  
 Clinical Research Support System, 415  
 cluster analysis  
     developmental trajectories, 211, 217–223  
     discrete *versus* continuous phenomena in, 219  
     static *versus* dynamic, 219–220, 232  
     within-class variability in, 220–221, 233  
 CNS (central nervous system), 344, 348, 353, 354  
 CNZ (Christchurch, New Zealand) study, 266  
 cocaine, 374, 456–457  
 cocaine- and amphetamine-regulated transcript (CART), 36  
 coexpression of receptors, 141, 142

- COGA (Collaborative Studies on Genetics of Alcoholism), 266
- cognition changes, 163–164
- cognitive control, 403, 424–425, 432–438
- during adolescence, 380
  - alertness in, 361
  - electrophysiological measures, 425–432
  - as endophenotype measurements, 358, 360
  - impairment, 113
  - impulsivity and, 112, 378–379
  - physiological basis of, 381
- cognitive deficits reversal, 434–435
- cognitive measures, of craving, 440
- cohorts
- effects of, 515
  - research models for, 519
- Collaborative Studies on Genetics of Alcoholism (COGA), 266
- colorectal polyps, 542
- commercial testing, 50
- common pathway model, 252, 270
- common-vulnerability model, 291–294, 306, 315–316
- communication of genetic findings, issues in, 45–50
- comorbidity
- psychiatric (*See* psychiatric comorbidity)
  - substance-use (*See* substance-use comorbidity)
- complementary dimensions of dependence, 97
- complex traits
- defining features, 31
  - genetic factors in, 35
  - genome-wide association studies for, 46
  - multiple determinations of, 22
  - replication difficulties, 45
  - sensitive genetic measures, 341
  - similarity of, 24–25
- Composite International Diagnostic Interview (CIDI), 81
- compulsive smoking, 80
- computational symbolic theory, 559–560
- COMT* gene, 269, 408–409, 430
- concurrent choice procedure, 416
- conditional independence, 256
- conditional triggers to smoke, 588
- conditioned place preference (CPP)
- biological plausibility of, 372–374, 421
  - in mice, 157–158, 161, 422
  - in rats, 423
- conditioning, contextual, 163–164
- conduct disorder
- adolescent smoking and, 201, 211, 232
  - definition of, 357
  - substance use and, 292–293, 304
- confounding factors, 32
- consensus, across indicators, 77
- constitutional hypothesis, 24
- construct
- definition of, 75
  - emerging, 520
  - proximal, 522
  - refinement of, 25–27
- construct properties, 75
- construct validation, 33, 34, 35, 75–78
- consumption level
- during adolescence, as indicator of adult dependence, 230–231
  - adolescent nicotine dependence and, 193
  - assessment of, 415, 418
- contamination, during administration, 145
- context-sensitive physiological measures, 363
- contextual conditioning, 163–164
- contingency table, smoking-drinking, 313, 315–316
- contingent factors, 247
- continuant, 541, 559
- continuous factors, 256
- continuous-level information, for behavioral modeling, 247
- continuous performance task (CPT), 362, 378, 433
- continuous phenomena, *versus* discrete phenomena, 219
- control, endophenotype measures of, 357–362
- control-related risk, 339, 354–357, 362
- controls, in association analysis, 258
- copy-number variation, 36
- core criteria, 76, 77
- core dependence dimension, 87–95
- core factors, 97, 168
- core strategy, 510
- cortisol, 447
- co-segregation of smoking behaviors, 24
- cost(s)
- genetic testing, 50
  - smoking cessation, 593
  - tobacco use, 4, 21
- COT (children of twins) design, 251–252, 279, 511
- cotinine
- biological activity of, 148
  - clearance factors, 39–40

- as nicotine by-product, 406
  - covariance, 32, 95–96, 341–342
    - in latent growth curve models, 254–255
    - in structural equation modeling, 248, 250
  - CPD. *See* cigarettes per day
  - CPP. *See* conditioned place preference
  - CPT (continuous performance task), 362, 378, 433
  - craving, 438–443
    - abstinence-induced (*See* abstinence-induced craving)
    - in adolescents, 192
    - cue-induced (*See* cue-induced craving)
    - dopaminergic systems associated with, 111
    - effects of, 405
    - measurement of, 403, 439–440
  - Craving subscale, 90–91
  - CREB activation, 160–161
  - CREB mice, 422
  - critical constituents, 25
  - cross-cultural differences, 515–516
  - cross-sectional studies, of substance-use comorbidity, 291
  - cross-species analysis, 348
  - cue(s)
    - in animal studies, 411
    - relapse, 99
    - reward signaling, 350
  - cue-induced craving, 438–439
    - with dependence, 441–443
    - effects of, 405
    - future research directions, 456–457
    - measurements, 403
    - physiological basis of, 111, 588
    - procedures to elicit, 440–441
    - research limitations in, 456
  - cue-self-administration response, 94
  - cultural transmission
    - adolescent smoking and, 198
    - effects of, 515
    - as environmental factor, 21
    - phenotypic, 251
    - research models for, 519
    - twin studies of, 262
  - cumulative effects, of pathogens, 103
  - cumulative risk, measurement of, 35
  - CYP2A6* gene
    - adolescent smoking and, 199
    - analysis of, 554, 555
    - association analysis of, 268
    - coding for, 408–409
    - mood effects with, 376
    - in nicotine metabolism, 22, 39–40, 149, 342, 406
    - in smokers, 413
    - variants in, 371, 418
  - Cyp2a5* gene variants, 149, 155, 413
  - CYP2B6* gene, 39
  - CYP2D6* gene, 39
  - Cys-Cys pairs, 136
  - cytochrome P-450 (CYP) system, 268
- D**
- danger-alarm responses, 353, 354
  - data-mining techniques, 541–542
  - data sets
    - ATBC analysis, 495
    - NHANES III analysis, 500–501
    - smoking cessation analysis, 493–494, 494
    - TUS-CPS analysis, 498
  - DAT/SLC6A3 (dopamine transporter protein), 268
  - DBA/2 inbred mice
    - conditioned place preference, 422
    - dose-dependent effects, 165
    - IV self-administration, 156
    - nicotine consumption, 159
    - nicotine effects, 435
    - oral self-administration, 412
    - prepulse inhibition in, 430–431
    - strain comparisons, 153–154, 164–165
    - tolerance in, 162, 163
  - DDC (DOPA decarboxylase), 269
  - definition variables, in structural equation modeling, 248
  - dehydroepiandrosterone (DHEA), 447
  - delay discounting
    - definition of, 348
    - in impulsivity, 349, 449, 450–452
    - physiological basis of, 379
    - study subjects for, 350
  - deleterious effect prediction, 554
  - dependence. *See also* nicotine dependence
    - addiction as, 77
    - core features of, 592
    - definition of, 75
    - distal measures of (*See* distal measures)
    - maintenance of, 598
    - model evaluation of, 78
    - patterns, 94



- severity with comorbidity, 98
- study of, 24
- depression, 351–352
  - nicotine amelioration and, 443
  - smoking association with, 444
  - subthreshold, 352
- desensitization, 146
- developmental pathways, 100, 589
  - impact on trajectory study, 222
- developmental psychopathology, 191–202, 292–293
- developmental trajectories. *See* adolescent developmental trajectories
- DH $\beta$ E, 159, 169
- DHEA (dehydroepiandrosterone), 447
- diabetes mellitus, 46
- Diagnostic and Statistical Manual of Mental Disorders (DSM)* criteria
  - adolescent smoking, 192, 264
  - attention deficit hyperactivity disorder, 356
  - dependence, 37–38, 40, 81, 86
  - poor agreement with FTND, 25–26
  - scales in, 79
  - substance-use disorder, 291
  - as syndromal medical model, 80–81
- diagnostic criteria, heritability of, 30, 38
- diagnostic inferences, 77
- Diagnostic Interview Schedule (DIS), 501
- diary prompts/responses, 527, 528–529, 530
- Digit Span test, 433
- diltiazem, 168
- direct drug infusion, 152–153
- direct-to-consumer marketing, 50
- DIS (Diagnostic Interview Schedule), 81, 501
- disadvantaged youth, 520
- discrete phenomena, *versus* continuous phenomena, 219
- discrimination, against nicotine dependence, 46–47, 49
- discriminative validity, 77
- discussion groups (OBO Foundry project), 560
- Disease Ontology (DO), 560
- disease risk, 541, 550
- disinhibition, common trait of, 292–293
- disorder markers, 107
- dispositional tolerance
  - acquisition of, 162
  - versus* behavioral tolerance, 164
  - in tolerance, 168
- distal influence, *versus* proximal influence, 519–522
- distal measures
  - agreement among, 88
  - early *versus* mature states, 74
  - genetic mapping, 78–81, 86–87, 103–105
  - versus* proximal measures, 516
- distress tolerance, 448
- distributional assumptions
  - in growth curve models, 255
  - in structural equation modeling, 249
- DNA methylation, 36
- DNA sequences analysis, 554
- DO (Disease Ontology), 560
- DOPA decarboxylase (DDC), 269
- dopamine
  - in attention deficit hyperactivity disorder, 356
  - attention-vigilance associations with, 434
  - impulsivity linkage with, 451–452
  - inactivation of, 430
  - mesotelecephalic, 171
  - midbrain circuits, 348, 349, 350
  - in nicotine binding role, 406–407
  - in nicotine dependence, 43, 410
  - receptors, 156, 343
  - regulation of, 540
  - reinforcement role of, 374, 407
  - reward pathways, 342, 349, 352
  - signaling, 160
- dopamine  $\beta$ -hydroxylase (DBH), 269
- dopamine hypothesis of dependence, 588
- dopaminergic neurons, in ventral tegmental area, 588
- dopaminergic systems
  - adolescent smoking and, 198–199, 201
  - association analysis of, 268–269
  - craving associated with, 111
- dopamine transporter protein (DAT/SLC6A3), 268
- dopamine transporter (*SLC6A3*) \*9-repeat allele, 441
- dose of nicotine, 161, 165
  - differences in, 367, 416
  - distribution of, 370
  - standardization, 152
- dose-response curve, 162, 444
- double variant haplotype, 545
- downregulation, 144–145, 588
- downstream processes, 81–82, 106
- DRD4 (dopamine receptor), 268
- DRD5 (dopamine receptor), 268
- DRD4* exon III polymorphism, 199



- DRD2* gene, 409  
 addiction association with, 32  
 coding for, 408  
 commercial testing for, 50  
 dependence association with, 407  
 in craving, 441  
 variants, 198
- DRD4\*7*-repeat allele, 376
- drinking. *See* alcohol use
- drinking-water administration, 147–148, 172
- drug addiction. *See* addiction; substance use; *specific drug*
- drug-motivated behavior, 404
- drug response comparison, 490–492, 491
- DSM. *See* *Diagnostic and Statistical Manual of Mental Disorders* criteria
- dual-trajectory model, of smoking-drinking trajectories, 315–316
- dynamic clustering  
*versus* static clustering, 219–220, 232  
 within-class variability in, 220–221, 233
- E**
- early-emergent motive, 91
- early-onset smokers  
 risk for persistence, 200, 212–213, 230–231  
 substance use and, 292, 296–297, 315, 320
- early smoking experiences (ESE), 375
- early tobacco exposure, 101, 155
- ecological momentary assessment (EMA), 255, 525
- economic deprivation, 520
- educational attainment, adolescent smoking and, 227–228, 232
- Edwards's theory of alcohol dependence syndrome, 82–83
- EEA (equal environments assumption), 516–517
- EEG (electroencephalogram), 354, 403, 425–427
- effortful control, 358
- elasticity of demand, 417
- elation, 374
- electroencephalogram (EEG), 354, 403, 425–427
- electromyography (EMG), 431
- electrophysiological measures, 378, 425–432
- EMA (ecological momentary assessment), 255, 525
- EMG (electromyography), 431
- empirical-Bayes approach, 549, 551
- empirical search strategies, 117
- employment discrimination, 49
- employment status, of hard-core smokers, 35
- encoding prior knowledge, 571
- endogenous cannabinoid systems, 159, 160
- endogenous enkephalin system, 160
- endogenous event-related potentials (ERPs), 427
- endophenotypes, 5, 408–410  
 caveats, 110–111  
 characteristics of, 107–110  
 in chronic smokers (*See* chronic smoker endophenotypes)  
 conceptual issues, 381–383  
 criteria, 413  
 disorders associated with, 106  
 future research directions, 455–457, 594  
 gene linking in, 347, 409  
 measurement of, 349–351, 353–354, 355, 357–362  
 motivational effects, 452, 454–455  
 in network models, 558  
 nicotine dependence, 409, 453  
 phenotypes associated with, 5, 33–34  
 pre-exposure risk, 340–347  
 in psychiatric genetics research, 25  
 replicability of, 27  
 transitional, 107, 108, 200, 233  
 types of, 340
- enhanced clearance. *See* dispositional tolerance entities, 541, 559, 560
- environmental factors, 99–103. *See also* social context; *specific factor*  
 adolescent smoking, 196–197  
 comorbidity, 99  
 cue-induced craving, 438–439  
 enrichment, 36  
 in experimentation, 31  
 gender differences in, 38  
 gene expression variation from, 36–37  
 genetic factors in, 35, 515  
 importance of, 29  
 linkage analysis, 258  
 measurement of, 35  
 in nicotine dependence, 22, 23  
 nicotine use, 158  
 relative contribution of, 30  
 in smoking decline, 20  
 substance use, 294–295  
 twin studies, 251, 262, 279, 280
- environmental pathogens, 5, 25, 35

- epidemiology, 31–37  
 future research in, 594  
 genetic, 257  
 extended, 250–252, 262–269, 279, 280  
 hierarchical modeling in, 570–571  
 perspectives from, 514  
 phenotypic definitions in, 493  
 public health outcomes in, 492  
 triangle, 513
- epigenetics, 36
- epistasis, 32–33
- epistemology, 74, 77
- equal environments assumption (EEA), 516–517
- equifinality, 191, 220
- ERPs (event-related potentials), 403, 427
- ESE (early smoking experiences), 375
- ethanol, 412. *See also* alcohol use
- ethnic differences, in developmental trajectories, 213–214, 279
- etiological architecture, 510–511, 515–518, 519, 527, 530
- etiology  
 diverse, 82, 106  
 matrix of, 509  
 of phenotypic assay, 83  
 of symptoms, 78
- euphoria, 374
- Event Ontology (EVO), 560
- event-related potentials (ERPs), 403, 427
- EVO (Event Ontology), 560
- exchangeable classes, 551
- excitatory tone, 141
- executive function  
 cognitive control and, 379  
 definition of, 361  
 nicotine dependence and, 34
- Executive Order 13145, 49
- exogenous event-related potentials (ERPs), 427
- experimental design, basics of, 149–150
- experimentation  
 influences on, 31  
 progression from, 30
- exposure model, 365
- extended structural equation modeling (XSEM), 249
- extended twin family studies, 250–252, 262, 279, 280
- extra-nicotinic mechanisms, 156–157
- extraversion, 346, 348–349
- extreme group membership, 96, 97
- extreme groups  
 alternatives to, 116–118  
 constructing, 114–116
- eyeblink response, 448
- ## F
- factor analysis, 37–38, 265  
 consistency, 88  
 correlation among, 80, 87  
*DSM-IV* correspondence with, 103
- factor loadings, 271–278
- factor mixture model (FMM), 256
- factor models, 256
- Fagerström Test for Nicotine Dependence (FTND), 79–80  
 as assessment tool, 405  
 dependence criteria, 37–38  
 FTQ as precursor to, 24  
 linkage analysis, 40–42, 589  
 poor agreement with *DSM*, 25–26  
 reliability and validity of, 26, 79–80  
 scales in, 79  
 visuospatial attention association with, 434
- Fagerström Tolerance Questionnaire (FTQ), 79–80  
 for adolescent smoking, 192, 230–231, 264  
 as physical dependence measure, 79  
 startle response inconsistency, 448  
 in susceptibility loci mapping, 24  
 test-retest reliability, 26
- false discovery rates (FDRs), 542, 546, 570, 573
- false positive reports, 570
- familial resemblance, class membership for, 256–257
- family-based studies  
 design of, 518  
 ecological momentary assessment in, 526–527  
 heritability documentation, 28–29  
 new methodologies in, 521
- family dysfunction scores, 33
- family environment, adolescent smoking and, 196–197
- family history analysis, example of, 225, 230, 232
- fast-ionotropic nicotinic receptors, 136
- FDRs (false discovery rates), 542, 546, 570, 573
- fear conditioning, 169, 432, 435
- fear responses, 353, 354
- feeder stream influences, 81–82, 106

- female smokers. *See also* gender differences  
 adolescent, 343  
 blood pressure changes in, 448  
 nicotine-dependence factors, 37, 38, 99  
*OPRM1* gene in, 419  
 statistics on, 21  
 twin studies, 515, 517
- fetal nicotine exposure, 357
- FHS (Framingham Heart Study), 266
- final common pathway, 82, 93, 106
- finite mixture model, 256
- Finnish Twin Registry, 262
- Finn Twin16-25 study, 307–323  
 methods, 307–310  
 results, 310–323
- first experience with smoking. *See* initial sensitivity
- first-stage estimates, 572
- Fisher, Ronald Aylmer, 22, 24
- five choice serial reaction time task (5CSRRT), 432
- five-class solution, example of, 226
- fixed effects, 215–216
- flunarizine, 168
- FMM (factor mixture model), 256
- focused interaction testing framework, 542
- forced choice procedure, 416
- formal model, 541, 559
- Fosb knockout mice, 161
- Foundational Model of Anatomy, 560
- four-point Likert scale, 375
- Framingham Heart Study (FHS), 266
- F344 rats, 423
- FTND. *See* Fagerström Test for Nicotine Dependence
- FTQ. *See* Fagerström Tolerance Questionnaire
- future research. *See also specific topics*  
 crosscutting issues, 595–596  
 implications of, 588–591  
 understanding, 588–596
- G**
- $\gamma$ -aminobutyric acid (GABA), 157, 406–407
- $\gamma$ -aminobutyric acid receptors, 43
- GABA ( $\gamma$ -aminobutyric acid), 157, 406–407
- GABAergic interneurons, 142
- gateway theory of substance use, 292
- GAW (Genetic Analysis Workshops), 266
- gender differences. *See also* female smokers;  
 male smokers  
 adolescent smoking, 196, 199, 227–228, 260,  
 263–264, 342  
 animal studies, 155, 164  
 cross-cultural, 515  
 factor loadings by, 271–276  
 nasal spray use, 373  
 nicotine-dependence factors, 38, 99  
 nicotine-dependence heritability estimates,  
 279, 281  
*OPRM1* gene, 419  
 smoking initiation, 267  
 startle response, 378  
 substance-use comorbidity, 304  
 twin studies, 262, 517
- gender heterogeneity, 273–274, 276–278
- gene(s). *See also* candidate gene studies  
 endophenotype linkage risks, 347, 409  
 in nicotine dependence, 32, 43
- gene-environment interaction, 33, 515  
 adolescent smoking, 197–200, 259, 346  
 biological process initiation, 591  
 environmental pathogens in, 25  
 in etiology, 509  
 investigation of, 546  
 substance-use comorbidity, 320  
 underuse of, 5
- gene expression, 36–37
- gene-gene interaction, 199, 343, 546
- gene-nicotine dependence associations, 45–46
- Gene Ontology, 560
- gene-pathogen relations, 100–101
- general growth mixture modeling (GGMM), 308–311
- generational changes, in smoking, 515
- Genes, Environment and Health Initiative, 531
- genetically informative designs, 527
- genetically modified mice, 444
- Genetic Analysis Workshops (GAW), 266
- genetic architecture, 510
- genetic association studies, 554, 556–559
- genetic drift, 150
- genetic epidemiology, 257  
 extended, 250–252, 262–269, 279, 280
- genetic factors  
 acute tolerance, 162–163  
 conditioned place preference, 159  
 craving, 441  
 detection of, 493

- in experimentation, 31
- importance of, 29
- measured, 4
- in nicotine effects, 22, 39–40, 539
- quantitative models, 512
- in reinforcement, 418
- relative contribution of, 30
- selecting for, 96–97
- genetic heterogeneity, 32
  - adolescent smoking initiation, 196, 201–202, 233
  - in developmental trajectories, 190, 233–234
  - gender, 273–274, 276–278
  - phenotypes, 341
  - population, 217
    - estimating, 218, 221–222
  - receptor, 139
- genetic heterogeneity models, difference in fit
  - between homogeneity models and, 274–275
- Genetic Information Nondiscrimination Act (GINA), 49
- genetic latent class models. *See* latent class analysis
- genetic latent growth curve models. *See* latent growth curve models
- genetic mapping, 73–75. *See also* phenotypic research
  - analytic strategies, 96–103
  - construct validation, 75–78
  - core dependence dimension, 87–95
  - covariation among measures, 95–96
  - distal measures of dependence, 78–81, 86–87, 103–105
  - multidimensional measures, 81–86
  - person factors implications in, 97–98
- genetic modeling, 245–281
  - methodological and conceptual issues, 247–248
  - statistical framework for, 248–259
- genetic polymorphism effects, 553–554
- genetic substrata, associated with tolerance, 162
- genetic testing, 46, 50
- genetic variants
  - biological processes associated with, 109
  - causal, 546
  - disease association with, 550
  - evaluation context for dependence, 76
  - phenotypes with, 102, 106, 109, 111
  - pleiotropic associations of, 47–50
  - selection of, 101
  - value of, 110
- gene-to-phenotype influence, 78
- gene-transcription cascades, 169
- genome(s)
  - candidate genes in, 24
  - data, 561
  - studies of, 589
- genome markers, linkage analysis, 257–258
- genome scan, 266–267
- genome-wide association studies (GWAS), 25, 44, 269
  - event-related potentials, 428, 430
  - FTND, 42–45
  - genetic variant findings, 589
  - genotyping technologies used in, 258–259
  - potential of, 45–46
  - results from, 342
  - susceptibility loci identification, 407–408
- genotyping
  - effects of variables on, 553
  - mouse strains, 150
  - P450, 39
  - with phase interaction, 545
  - phenotypes and, 560–562
  - technologies, 257–259
- geographic information systems (GIS), 520–521
- GGMM (general growth mixture modeling), 308–311
- GINA (Genetic Information Nondiscrimination Act), 49
- GIS (geographic information systems), 520–521
- global use, 4, 21
- GluR (glutamate receptor), 157, 169
- glutamate receptor (GluR), 157, 169
- GMM (growth mixture modeling), 202, 218, 221, 308
- go/no-go task, 358–359, 451
- government policies, 7, 20
  - effect on adolescent smoking, 193
  - substance use, 294–295
- grant funding, 45–46
- graph connectivity, 571
- grouping variables, for growth curve modeling, 216–217, 232–233
- group membership, stability of, across statistical models, 229–230
- growth curve, nonlinear, 255
- growth curve mixture modeling, 215–217, 248–249
- growth mixture modeling (GMM), 202, 218, 221, 308

growth process, random effects for, 220–221  
 gum. *See* nicotine gum  
 gustatory reaction to tobacco, 75, 84  
 GWAS. *See* genome-wide association studies

## H

habituation, *versus* addiction, 24  
 half-life of nicotine, 147  
 haplotypes
 

- dependence and, 100
- disease association with, 544
- double variant, 545

 hard-core smokers, characteristics of, 35–36  
 Hardy-Weinberg equilibrium, 545  
 head rush, 374  
 health care access, disparities in, 47  
 health effects of smoking, statistics on, 4, 21  
 heart rate, 351, 354, 440, 447  
 Heaviness of Smoking Index (HSI)
 

- components of, 37, 413
- predictive value of, 80, 89–90
- scales in, 79
- zero-order correlations in, 80

 heavy smokers, 93
 

- delay discounting, 350
- diagnostic variance in, 89
- genetic factors in, 29
- versus* light smokers, 43, 81, 83–84, 90, 94
- substance use and, 296–297, 315

 Heavy Smoking Index, 265  
 hedonic impact of nicotine, 158, 372, 424  
 heritability
 

- adolescent nicotine dependence, 86, 342
- antisocial scores, 33
- anxiety, 445
- delay aversion, 351
- dependence, 37–38, 86, 433–434
- diagnostic criteria, 30, 38
- endophenotypes, 107
- estimates, 29–30
- event-related potential, 428, 429–430
- factors in, 28–29
- gender differences in, 279, 281
- impulsivity, 451
- neuroticism, 101
- nicotine metabolism/clearance, 38–40
- P450 genotype, 39
- prepulse inhibition startle response, 431–432
- response inhibition, 359
- resting EEG, 426
- smoking cessation, 406
- smoking heaviness, 90
- withdrawal symptoms, 30
- working memory, 437

 heterogeneity. *See* genetic heterogeneity  
 hierarchical modeling
 

- estimation for, 575–576
- with ontologies, 551–552
- with prior knowledge, 570
- for statistical modeling, 117
- stochastic variable selection and, 547–549, 572, 573
- weighting in, 570

 high-affinity nAChRs, 156, 159  
 higher-order joint actions, 546  
 high genetic proneness, 96  
 hippocampal activity, 141, 142  
 HISTONE proteins, 36  
 home smoking bans, 99  
 homogeneity models, 271
 

- difference in fit between heterogeneity models and, 274–275

 homogeneous population
 

- assumption of, 248
- for growth curve modeling, 216–217

 Hooked on Nicotine Checklist, 26  
 Horn-Russell Scale, 34  
 hostility, 357, 362, 377  
 Household Adult Questionnaire, 501  
 HSI. *See* Heaviness of Smoking Index  
*HTR5A* gene, 42  
*5-HTT* gene, 33, 269, 441  
*5-HTTLPR* gene, 101, 199, 409
 

- in adolescent girls, 343
- in affective response, 112, 446
- coding for, 408

 human clinical research
 

- affective regulation, 444–445
- electrophysiological measures, 426
- event-related potential, 428
- impulsivity, 450
- reinforcement, 413–414

 HumanCyc database, 556  
 human genome, similarity with mice genome, 134  
 3-hydroxycotinine, 406  
 hyperactivity, 354, 356  
 hypertensive rats, 449

- I**  
 IBD (identical by descent), 257, 258  
 ICD-10 criteria, 80–81, 192  
 ICR mice, 159, 162, 163  
 ICSS (intracranial self-stimulation), 372–373, 421  
 identical by descent (IBD), 257, 258  
 illicit substances. *See* substance use; *specific drug*  
 impulse control, 449–452  
 impulsivity, 348  
   in attention deficit hyperactivity disorder, 354, 356  
   clinical research, 433, 450–451  
   cognitive control and, 112, 378–379  
   delay discounting with, 349, 350, 449, 450–452  
   heritability, 451  
   measurement of, 450–451  
   neural incentive system association, 346  
   preclinical research, 449–450  
   in response inhibition, 359  
 incubation effect of initial exposure, 371  
 independent pathway model, 253  
 Indiana University Smoking Survey, 223–233  
   data analysis, 225–226  
   discussion, 231–233  
   measures, 224–225  
   procedures, 224  
   results, 226–231  
 individual pathways to mature state, 105, 106  
 “infectious disease” model, 522  
 inflammation masking, 145  
 inhibitors. *See* antagonists  
 inhibitory interneurons, 141, 142  
 initial exposure response measures, 339  
 initial sensitivity, 27, 363–364  
   future research directions, 380–381  
   innate sensitivity, 364–368  
   other responses, 373–380  
   reinforcement, 368–372  
   rewards, 372–373  
 innate sensitivity, 364–368  
 instrumental learning, 158  
 insurance companies, genetic testing and, 49  
 integrative model of nicotine dependence, 22, 23  
 integrative theory of triadic influence, 293  
 intercept, distribution of, 219, 306, 310  
 intercept models, initiation-based, 322  
 intermediate phenotypes, 341, 342. *See also* endophenotypes  
  
*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) criteria, 80–81, 192  
 interpersonal dynamics, 517, 522–525  
 interval level, 247  
 intracranial self-stimulation (ICSS), 372–373, 421  
 intrathecal administration, 162  
 intrauterine events, 100  
 intravenous administration, 146  
   humans, 415  
   rodents, 152–157, 410–412  
 in utero nicotine exposure, 357  
 inveterate smokers, 87  
 ion-channel receptors, 143  
 Iowa gambling task, 350  
 IRT. *See* item response theory  
 item difficulty, 270  
 item response theory (IRT), 254  
   empirical example of, 269–279  
   *versus* sum score approach, 278  
  
**J**  
 Jarvik, Murray, 24  
 journal publishing requirements, 45–46  
  
**K**  
 kinship model, twin studies extended to, 250–252, 262, 279, 280  
*k*-means clustering, 217  
 knockout mice, 159, 160, 161, 166, 422  
 Kraepelinian approach to diagnosis, 291  
 Kyoto Encyclopedia of Genes and Genomes, 561  
  
**L**  
 laboratory-based measurements  
   attention deficit hyperactivity disorder, 356  
   consumption, 418  
   endophenotypes, 349–351, 353–354, 357–362  
 late emergent symptoms, 90–91  
 latency to first puff, 415  
 latent class analysis, 80, 92, 98, 248–249, 256–257, 266, 280  
 latent class growth analysis (LCGA), 218, 226–229, 248–249  
 latent growth curve (LGC) models, 254–256, 266, 280

- association data integrated into, 259
  - substance-use comorbidity, 306, 308, 321
  - latent phenotype model, 252, 270
  - latent profile modeling, 90–91
  - latent trait, 270
  - latent variables, 77, 248, 256
    - substance-use comorbidity, 306, 321, 324
  - LCGA (latent class growth analysis), 218, 226–229, 248–249
  - LD (linkage disequilibrium), 543, 545–546
  - learning associations, 349
  - learning differences, 158, 169
  - letter cancellation task, 433
  - level, in latent growth curve models, 254
  - Lewis rats, 411, 423
  - LGC. *See* latent growth curve models
  - liability models, of smoking behavior stages, 264, 280
  - lifetime regular smoking, definition of, 29
  - ligand-activated ion channels, 143
  - light smoking. *See* chippers
  - likelihood-based approaches, in cluster analysis, 217–218
  - likelihood ratio tests, 310, 312–313
  - linear growth, assumption of, 255
  - linear model, 116
  - linear regression, in structural equation modeling, 248
  - linear relations, 25
  - linkage analysis, 257–258, 266–268
    - candidate gene studies, 32, 40–42, 267–268, 280–281, 589
    - environmental factors, 258
    - genome markers, 24, 257–258
    - nicotine-dependence indices, 40–42
  - linkage disequilibrium (LD), 543, 545–546
  - Lister rats, 432–433, 444
  - lithium-chloride conditioned place aversion, 161
  - liver cytochrome P-450 enzyme CYP2A6. *See* CYP2A6 gene
  - location of smoking, 527
  - loci segregation, 40
  - locomotor activity, 369, 422
  - logarithm of odds (LOD) score, 40–42, 258, 267
  - logistic regression curves, 91
  - Long-Evans rats, 411
  - longitudinal data
    - growth curve modeling of, 218–219, 234
    - on substance-use comorbidity, 291, 320
  - Loss of Control subscale, 90–91
  - low genetic proneness, 96
  - LPAAT-delta gene, 42
  - lung, nicotine concentration in, 145
  - lung cancer, predisposition to, 44, 50
- ## M
- macrocontextual factors, 509, 514
    - as moderators, 515–516
  - macroenvironment proximal indicators, 521–522
  - macular degeneration, age-related, 46
  - magnetic resonance imaging (MRI), 351, 439, 456–457
  - maintenance of dependence, 589
  - male smokers. *See also* gender differences
    - adolescent, 342, 348
    - blood pressure changes in, 449
    - nicotine-dependence factors, 37, 38, 99
    - OPRM1 gene in, 419
    - statistics on, 21
    - twin studies, 515, 517
  - manifestations of dependence, 75
  - Mannheim Study of Risk Children, 199
  - MAO. *See* monoamine oxidase
  - MAP3K4 gene, 42
  - marginalization
    - of smoking, 4, 21
    - of social groups, 47
  - marginal nonnormality, 221
  - marijuana use
    - early pleasurable, 374
    - tobacco use concurrently with, trajectories of, 296–298
    - modeling, 304–305
    - trajectories of, 295–296
  - marketing direct-to-consumer, 50
  - Markov chain Monte Carlo (MCMC) methods, 542
  - masking etiology, 82
  - masking of causal factors, 74
  - maternal care, 36
  - mature subphenotypes, 82, 110–111
  - maximum acute tolerance, 162, 165
  - maximum price assessment, 418
  - McGill University Study on the National History of Nicotine Dependence, 199
  - MCMC (Markov chain Monte Carlo) methods, 542
  - mean (centroid)
    - cluster analysis, 217
    - growth curve modeling, 255
    - structural equation modeling, 248–249



- measured genetic factors, 4  
measurement invariance, 247, 255, 276, 280  
mecamylamine, 159  
mediation  
  of conditioned place preference, 161  
  by endophenotypes, 107–108  
  of nicotine, 160  
memantine, 156, 171  
memory, 379, 434–438  
Mendelian randomization, 118  
mesolimbic dopaminergic system, 410, 411  
metabolic tolerance, 97  
metabotropic glutamate receptor 5 (mGluR5), 156  
methodological issues  
  assessment precision, 520  
  behavioral modeling, 247–248  
  family-based studies, 521  
  future research directions, 383–384, 594  
  genetic modeling, 247–248  
  innate sensitivity research, 366–368  
  real-time interaction, 524–525  
  research limitations, 366–368, 376, 383–384  
  substance-use comorbidity, 321–323  
methyllycaconitine citrate (MLA), 159  
mGluR5 (metabotropic glutamate receptor 5), 156  
mice. *See* mouse models  
microchip analysis, 170, 258–259  
microcontextual factors, 509, 514  
  coding of real-time interaction, 524  
  as moderators, 516–518  
microsatellites, 543, 551  
microsocial context, quantifying, 522–525  
midbrain dopamine circuits, 348, 349  
Mid-South Tobacco Family (MSTF), 267  
migration levels, 516  
Minnesota Nicotine Withdrawal Scale, 446  
Minnesota Twin Family Study (MTFS), 196, 260, 360  
mirror tracing, 448  
misleading claims, 50  
misspecification, model, 222  
mixed models, developmental trajectories, 215  
MLA (methyllycaconitine citrate), 159  
model(s)  
  clarification of, 559  
  searching, 551  
  selection of, 547  
  with stochastic variable selection, 549–550, 551–552  
model fit, evaluation of, 310, 312–313  
modeling. *See also specific types of modeling*  
  phenotype (*See* phenotype modeling)  
  with prior knowledge, 570  
  selection algorithm, 577–578  
  uncertainties in, 546, 547, 549  
model misspecification, 222  
moderation of relationships, 248  
modified pairwise interaction, 545  
modulation  
  dopamine receptors, 156  
  nicotine rewards, 160  
molecular genetic studies, 266  
  of adolescent smoking, 198–199  
  analytic framework for, 257–259  
Monitoring the Future project, 299, 304  
monoamine oxidase (MAO)  
  in anxiety disorders, 353  
  neuroticism and, 351  
  in neurotransmitter breakdown, 540  
monoamine oxidase (*MAOA/MAOB*) gene, 269  
mood effects, 373–376, 380–381  
  in ATBC analysis, 497  
  measures of, 372  
  of nicotine, 366  
Mood Form of Diener and Emmons, 374–375, 446  
morning smoking. *See* time to first cigarette  
morphine, as nicotine substitute, 153  
Morris water maze, 435  
mortality statistics, 4, 21  
motivational mechanisms, 84, 403, 408  
  reinforcement, 410–420  
  rewards, 420–424  
Mouse Genome Informatics database, 150  
mouse models, 134–135, 418  
  adolescent exposure, 194–195  
  behavioral changes, 151–157  
  future research directions, 168–172  
  nicotine administration, 145–149  
  nicotine dependence, 149–151  
  nicotinic receptors, 135  
    customizing, 141–143  
    functional diversity of, 136–141  
    molecular biology of, 136  
    nicotine as agonist/antagonist, 143–144  
    upregulation, 144–145  
  reward, 157–161  
  startle inconsistency, 444  
  strains, 134 (*See also* strain-specific differences; *specific strain*)  
    research options with, 592  
    selection of, 150–151

- tolerance, 162–168  
 mouse-rat differences, 150  
 movies, smoking in, 7, 20, 523  
 MRI (magnetic resonance imaging), 351, 439, 456–457  
 MSTF (Mid-South Tobacco Family), 267  
 MTFS (Minnesota Twin Family Study), 196, 260, 360  
 multidimensional measures, of nicotine dependence, 81–86  
 multifinality, 191  
 multilevel analysis, difficulties of, 248  
 multiple trajectories, developmental, 191–202, 232–234  
 multivariate analysis  
     developmental trajectories, 215  
     latent growth curve models, 255  
     substance-use comorbidity, 315–316, 321  
     twin studies, 262–263  
 multivariate factor model, 252–253  
 multivariate normal distribution  
     in growth curve models, 255  
     in structural equation modeling, 249  
 multivariate normality, within-class, 221, 233  
 mu opioid knockout mice, 422  
 mu opioid receptors  
     in conditioned place preference, 160  
     in nicotine replacement therapy, 407  
     reward mediation, 419  
     in tolerance, 167, 168  
 muscarinic acetylcholinergic systems, 166, 168  
 muscarinic receptors  
     in aging, 170  
     blockading, 140–141  
     metabotropic, 136  
 muscle tension, 377–378  
 mutations  
     rate predictions, 554  
     for tolerance, 166  
 Muthén, Bengt, 218
- N**
- nAChRs. *See* nicotinic acetylcholine receptors  
 Nagin, Daniel, 218  
 naloxone, 160  
 nasal spray. *See* nicotine nasal spray  
 National Cancer Institute, 498  
 National Center for Biomedical Ontology (NCBO), 561  
 National Comorbidity Study, 445  
 National Health and Nutrition Examination Survey (NHANES III), 487, 494, 500–503  
 National Institute of Mental Health Diagnostic Interview Schedule (DIS), 81, 501  
 National Institute on Drug Abuse Genetics Consortium, 43  
 National Institutes of Health, 531  
 National Longitudinal Study of Adolescent Health (Add Health), 197–198, 261, 517  
 National Survey on Drug Use and Health, 93  
 N-back task, 436  
 NCBO (National Center for Biomedical Ontology), 561  
 NDSS. *See* Nicotine Dependence Syndrome Scale  
 NEAD (Nonshared Environment in Adolescent Development) Project, 509, 524–525  
 Netherlands Twin Register, 262  
 Netherlands Twin Study of Anxious Depression (NETSAD), 266–267  
 network models, 554, 556–558  
 neural analysis, 349–351, 353–354, 357–362  
 neural incentive system, 346  
 neural networks modeling, 340–341  
 neural substrata, associated with tolerance, 162  
 neural systems, candidate, 343–346  
 neurexin 1 (*NRXN1*) gene, 43  
 neurobiological analysis, 348  
 neurobiological dependence pathways, 43  
 neurobiological systems, 344  
 neuroendocrine response, to stress, 354  
 neuroimaging, 360, 379–380  
 neuropeptide systems, 159, 160  
 neuroprotection, 170  
 neuroticism, 101, 351–353  
 neurotransmitter systems  
     in chronic tolerance, 166–167  
     in conditioned place preference, 159–161  
 New England Family Study, 526  
 NHANES III (National Health and Nutrition Examination Survey), 487, 494, 500–503  
 nicotine  
     administration of (*See* administration)  
     age-related response differences, 194–195  
     as agonist/antagonist, 143–144  
     anti-inflammatory effects of, 148–149  
     anxiogenic effects of, 168  
     behavioral changes from, 151–157  
     bioavailability of, 7, 20  
     enforcement timing, 369  
     in free-base form, 148

- frequency of use, 4, 21, 369–371, 413, 420
- hedonic impact of, 158, 372, 424
- neuronal activity induced by, 43
- physical changes from, 162
- pre-exposure risk (*See* pre-exposure risk)
- pretreatment, 420
- reinforcement (*See* reinforcement)
- rewards and (*See* reward)
- tolerance (*See* tolerance)
- nicotine aerosols, 147
- nicotine-binding sites, 135, 144
- nicotine choice, 369
- nicotine choice procedure, 416, 419–420
- nicotine cigarette choice paradigm, 419
- nicotine clearance
  - dispositional tolerance, 162, 164, 168
  - genetic factors in, 39–40, 539
- nicotine dependence, 20–22, 149–151
  - in adolescence (*See* adolescent nicotine dependence)
  - concurrent with substance use (*See* substance-use comorbidity)
  - construct refinement, 25–27
  - craving associated with (*See* craving)
  - crosscutting issues, 595–596
  - developmental pathways in, 589
  - distal measures of (*See* distal measures)
  - endophenotypes in, 409, 453
  - epidemiological concepts, 31–37
  - future research directions, 455–457
  - heritability of (*See* genetic factors; heritability)
  - historical perspective of, 22–25
  - inference of, 77
  - mouse models of (*See* mouse models)
  - phenotype (*See* phenotype(s))
  - progression research, 592
  - psychiatric disorders correlated with, 98
  - risk with, 375–376
  - smoking compared with, 87
  - versus* tobacco dependence, 75
  - treatment of (*See* smoking cessation)
  - understanding of, 588–596
- nicotine-dependence measures, 26, 28, 37–45, 73, 78, 79
  - adolescents, 192, 230–231, 264
  - example of, 225
  - invariance, 276, 280
- Nicotine Dependence Syndrome Scale (NDSS), 82–84
  - abbreviated, 500
  - as assessment tool, 405
  - subscales of, 90
  - in TUS-CPS analysis, 498
- nicotine deprivation memory deficits, 436
- nicotine gum
  - as consumption assessment, 415
  - effect on EEG activity, 426
  - in memory effects, 435
  - versus* placebo, 370
- nicotine metabolism
  - association analysis of, 268
  - catabolism of, 149
  - CPD variation and, 34
  - CYP2A6* gene in, 39–40, 149, 342, 406, 418
  - in dependence risk, 22, 342
  - in ontology example, 562–569
  - pathway, 556
- nicotine nasal spray
  - aversion with *DRD4\*7*-repeat allele, 376
  - as consumption assessment, 415
  - in current smokers, 374
  - memory effects of, 435–436
  - versus* placebo, 369–370
  - pleasurable responses to, 373
- nicotine patches
  - effect on EEG activity, 426
  - in memory effects, 435
  - on nonsmoking adults, 377
- Nicotine Pharmacokinetics Ontology (NPKO), 539, 561, 571
- nicotine replacement therapy (NRT), 406. *See also* smoking cessation
- nicotinic acetylcholine receptors (nAChRs), 134
  - association analysis, 268
  - as attention factor, 362
  - beta2-subunit (*CHRNA2*), 268
  - binding to, 588
  - blockading, 140–141, 143–144
  - chromosomal regions, 43, 44, 50
  - in chronic tolerance, 166–167
  - coding for, 408
  - customizing, 141–143
  - desensitization of, 146
  - fast-ionic, 136
  - functional diversity of, 136–141
  - high-affinity, 157
  - illustration, 409
  - as impulsivity mediator, 449
  - inactivation of, 143
  - inferences from, 152–153

- initial sensitivity response with, 376–377  
 molecular biology of, 136  
 in nicotine binding role, 406–407  
 in nicotine dependence, 411  
 structure of, 136–138, 138  
 tissue-specific responses, 71, 133  
 in tolerance, 168  
 upregulation of, 135, 144–145, 588
- nicotinic receptor subunits, 136–140  
*CHRNA5/CHRN3* genes, 342  
 composition of, 139  
 functional variants of, 140  
 limiting expression, 141–143  
 structure of, 136, 137
- nimodipine, 162, 167, 168
- nitric oxide, in conditioned place preference, 161
- 7-nitroindazole, 161
- N*-methyl-D-aspartic acid (NMDA) glutamate receptors, 156
- NMRI outbred mice, 154, 412, 430
- nomological net, 76
- noncoding DNA sequences, 554
- nonlinear growth curves, 255
- nonnicotinic systems, 166
- nonnormality, 221
- Nonshared Environment in Adolescent Development (NEAD) Project, 509, 524–525
- nonsmokers (abstainers)  
 characteristics of, 22  
 inclusion *versus* exclusion of, 222–223, 235, 323  
 nicotine patches, 377
- Northern California Twin Registry, 539, 540
- novelty seeking, 155–156, 199, 348–349  
 by adolescents, 27  
 nasal spray use in, 373  
 neural incentive system association with, 346  
 in substance use, 292–293, 348–349
- NPKO (Nicotine Pharmacokinetics Ontology), 539
- NRT (nicotine replacement therapy), 406. *See also* smoking cessation
- NRXN1* gene, 43
- NRXN3* gene, 43
- nutritional cancer prevention, 497
- O**
- OBO (Open Biomedical Ontologies), 560
- OBO-Edit, 561
- OBO Foundry project, 560
- OBO Relation Ontology, 561
- observed variables, in structural equation modeling, 248
- occurrent, 541, 559
- oddball stimulus, 429
- olanzapine, 456
- ontologies, 539–541  
 definition of, 541, 559  
 development process, 560–562  
 discussion of, 570–574  
 methods, 541–543, 550–562  
 nicotine metabolism, 562–569  
 statistical approaches, 543–550
- Ontology Web Language (OWL), 561
- Open Biomedical Ontologies (OBO), 560
- Open Source software, 561
- OPRM1* gene, 409  
 coding for, 408  
 gender differences in, 419  
 in nicotine replacement therapy, 407  
 in smokers, 423  
 support interval proximity, 42
- oral administration, 147–149, 172, 412–413
- oral mucosa exposure to nicotine, 148
- ordinal data, analytical framework for, 247, 255
- osmotic minipump, 147
- outcomes of dependence, 75
- outliers, controlling for, 281
- OWL (Ontology Web Language), 561
- oxotremorine, 166–167
- P**
- P3 amplitude, 294
- panic disorder, 353
- PANTHER Pathways databases, 556, 561
- parent(s)  
 educational level of, 519  
 twin studies extended to, 251, 262, 279, 280
- parental monitoring, as smoking counterforce, 22
- parental smoking  
 adolescent smoking and, 196–197, 200, 262, 346  
 behavioral modeling of, 246  
 nasal spray non-response, 377  
 smoke-free home with, 523  
 socialization effects from, 517
- parenting behavior, 342
- partition variation, 270, 280
- passive avoidance, 435
- patch. *See* nicotine patches

- path diagrams, in structural equation modeling, 248–250
- pathogen modeling, 100–101, 103
- PATO (Phenotype and Trait Ontology), 560, 571
- Pavlovian learning, 158
- PBT (problem behavior theory), 198, 292–294, 322
- PDAs (personal digital assistants), 525–527
- peers
- as influence, 100, 346, 517
  - as smoking predictors, 523
- peer smoking, effect on adolescent smoking, 197
- penetrance, incomplete, 31
- peripheral nervous system (PNS), 344, 348
- P50 ERP, 427–428
- persistence
- drug use, 417–418
  - negative affect with, 447
  - smoking (*See* smoking persistence)
- personal digital assistants (PDAs), 525–527
- personalized health care, 49–50
- person factors, 97–99
- PET (positron emission tomography), 439
- P300 event-related potential (ERP), 359–360, 429–430
- P450 genotype, 39
- pharmacokinetics, 37, 39, 118, 149, 542, 590
- pharmacokinetics ontology, 539, 561, 571
- phenotype(s)
- assays, 83
  - association of, 33
  - behavioral, 171, 492
  - characteristics of, 109
  - components, 341
  - developmental progression of, 74
  - effects of variables on, 553
  - as endophenotypes, 5, 33–34
  - environmental, 34–36
  - framework, 27–31
  - genetic mapping, 96–103
  - genetic variants to, 102
  - genotyping and, 560–562
  - heterogeneity, 341
  - intermediate, 341, 342 (*See also* endophenotypes)
  - of mouse strains, 150
  - pathways, 23, 590
  - as points in smoking trajectory, 490
  - research pitfalls, 489
  - stages, 109
  - substance-use disorders, 316–318, 321, 324
- Phenotype and Trait Ontology (PATO), 560, 571
- phenotype modeling, 487, 488–492
- examples, 493–503
  - methods, 492–494
  - summary, 503–505
- phenotypic assortative mating, 251
- phenotypic cultural transmission, 251
- phenotypic research, 105–106
- analytic strategies, 113–118
  - causal paths, 107–110, 111–113
  - caveats, 110–111
  - summary, 118–119
- phenylthiocarbamide (PTC) haplotype, 84
- phosphatase and tensin homolog (*PTEN*) gene, 269
- physical aggression, 357
- physical responses to nicotine, 169
- symptoms, 26
  - in tolerance, 162–163, 164–165
- physiological measures of response reward, 351
- physiological startle. *See* startle response
- physiology
- of affect, 377–378
  - of behavioral traits, 344, 345, 346
- Pittsburgh Youth Study, 214
- placebo, *versus* nicotine, 369–370, 420
- placenta, 145
- plasma nicotine levels
- with IV injection, 146
  - tissue nicotine levels compared with, 145
  - in tolerance studies, 163–164
- pleiotropy, 32, 47–50
- PNS (peripheral nervous system), 344, 348
- point mutation, 444
- policy interventions, 34–35
- polymorphisms, 553–554. *See also* single nucleotide polymorphism
- associations with, 116
  - different priors for, 571
  - in dopamine reward pathway, 342
  - emphasis within genes, 547
  - investigation of, 546–547
  - numerous, challenges of, 546–547
  - perturbations from, 554
  - trait variation effect of, 549
- PolyPhen (polymorphism phenotyping), 554
- polysubstance use, 43, 296
- population
- frequency of genetic factors in, 86

- for growth curve modeling, 216–217, 234
  - homogeneous, assumption of, 248
  - in latent class analysis, 256
  - response distribution in, 370, 373, 376–380
  - in structural equation modeling, 248–249
  - population heterogeneity, 217
    - estimating, 218, 221–222
  - Positive and Negative Affect Schedule, 374–375, 446
  - positron emission tomography (PET), 439
  - postural hypotension, 449
  - PPI (prepulse inhibition), 378, 403, 430–432
  - preclinical research. *See also* animal studies; mouse models
    - affective regulation, 443–444
    - electrophysiological measures, 425–426
    - event-related potential, 427–428
    - impulsivity, 449–450
    - reinforcement, 410
    - rewards, 421–423
  - precursors, class III phenotypes as, 30
  - predictive validity
    - of genetic testing, 50
    - of primary motives scales, 90–91
  - pre-exposure risk, 339, 340. *See also* smoking initiation and progression risk
    - endophenotypes, 340–347
    - future research directions, 381–385
    - initial sensitivity endophenotypes (*See* initial sensitivity)
  - preproenkephalin knockout mice, 160, 422
  - prepulse inhibition (PPI), 378, 403, 430–432
  - price-demand curve, 417
  - pricing, of tobacco products, 20, 21, 520
  - primary motive scales, as predictors, 90–93
  - prior covariate specification, 570–571
  - prior knowledge, ontologies and, 553–562
  - PR (progressive ratio) measures, 417–418, 420, 454
  - probability discounting, 450–451
  - problem behavior theory (PBT), 198, 292–294, 322
  - problem use, 196, 198, 263, 294
  - Profile of Mood States, 374–375, 446
  - programmed lapse procedure, 454
  - progression to smoking, 491
  - progressive ratio (PR) measures, 417–418, 420, 454
  - Project on Human Development in Chicago Neighborhoods, 520
  - “proof of concept” analyses, 493, 494
  - protective factors
    - in adolescents, 343
    - versus* vulnerabilities, 87, 114
  - protein sequence data, 561
  - protobacco advertising, 7, 20, 30, 348
  - prototypes, of nicotine-dependence research, 27–28
  - proximal indicators, 509
  - proximal influence, 519–522
  - proximal measures
    - versus* distal measures, 516
    - of social context, 518–527
  - psychiatric comorbidity, 81, 98–99
    - with *DSM-IV* dependence, 26, 81
    - empirical examples of, 496, 502
    - resolving, 115
  - psychiatric genetics research, 25, 27
  - psychoactive alkaloid, 22
  - psychological traits
    - approach-related risk, 346–349
    - avoidance-related risk, 351
    - control-related risk, 354–357
  - psychometric common factor model, 252
  - psychopathology
    - developmental, 191–202, 292–293
    - indices, 32
    - physiological basis of, 344
    - substance use and, 292–293, 304
  - psychophysiological responses
    - to acute stressors, 448–449
    - craving, 440
  - psychosocial factors
    - in adolescent nicotine dependence, 195
    - in adolescent smoking initiation, 200, 202, 211
  - PTC (phenylthiocarbamide) haplotype, 84
  - PTEN* gene, 269
  - public health messages, 47
  - public health outcomes, 492
  - public settings, smoking in, 4, 20–21
  - putative endophenotypes, 341
- Q**
- QSU (Questionnaire on Smoking Urges), 439
  - QTL (quantitative trait locus), 258
  - quantitative genetic models, 512, 522
  - quantitative trait locus (QTL), 258
  - quantity smoked measures, 28
  - Questionnaire on Smoking Urges (QSU), 439



## R

- racial background, 439. *See also* African Americans
- racism, associated with genetic information, 47
- random effects, 216  
within-class, 220–221, 233
- rapid-decision context, 358
- Rapid Visual Information Processing (RVIP) task, 433
- rat models  
adolescent nicotine exposure in, 194–195  
alcohol/nicotine correlation, 369  
conditioned place preference in, 423  
self-administration of electrical stimulation, 421  
sensitivity in, 364  
strains, 411 (*See also specific strain*)
- Reactome, 561
- real-time contexts, 526
- real-time interaction, 524–525
- recall, 379
- receptor heterogeneity, 139
- recovery, from acute tolerance, 162
- regression models, 248, 542, 543, 550–551, 572
- regular smoking  
definition of, 29  
genetic factors in, 29–30
- reinforcement, 151–152, 155–156, 366–372, 380  
alternative, 417  
in cognitive control, 349  
enhancing, 413  
genetic influences in, 418  
in initial sensitivity, 368–372  
measurement of, 414–420  
motivational mechanisms, 410–420  
secondary, 411, 413
- relapse  
environmental influences in, 95  
physiological basis of, 588  
predictors of, 77, 413, 434, 442, 444–445  
time to first cigarette as predictor of, 80, 89
- relations between entities, 541, 559, 560
- relative measurements, 571
- reliability. *See also* test-retest reliability  
of developmental trajectory research, 234  
of nicotine-dependence measures, 26, 79–80  
recall, 26–27
- reliability coefficients, 79
- religiosity, adolescent smoking and, 198
- repeated-measures data, developmental trajectories, 215, 222
- replication, of gene-nicotine dependence associations, 45–46
- research findings, communication of, issues in, 45–50
- research limitations  
adolescent smoking, 367  
adult smoking phenotype, 190  
ATBC analysis, 497, 504  
behavioral measures, 104  
cue-induced craving, 456  
data, 572  
distal measures, 103  
*DSM*, 103  
extreme groups, 114–116  
methodology, 366–368, 376, 383–384  
NHANES III analysis, 503–505  
nicotine-dependence measures, 103–104  
Nicotine Dependence Syndrome Scale, 84  
retrospective reporting, 367  
self-report measures, 367  
smoking cessation research, 454–455  
statistics modeling, 570  
tobacco dependence assessments, 95  
TUS-CPS analysis, 500, 504  
twin studies, 279–280  
Wisconsin Inventory of Smoking Dependence Motives, 85–86
- residual familial factors (F), 258
- residual item variances, 270
- respiratory sinus arrhythmia (RSA), 361
- response inhibition, 358–359
- resting EEG activity, 425–427
- retail tobacco outlets, 520, 521
- retrospective reporting limitations, 367
- reward, 157–161  
definition of, 349  
for depressed smokers, 352  
future research directions, 454–455  
immediacy over magnitude, 348, 349  
in initial sensitivity, 372–373  
measurement of, 351, 366, 372–373, 380, 423–424  
modulation of, 160  
motivational mechanisms, 420–424  
mu opioid receptor mediation, 419  
preclinical studies, 157–161, 372–373, 421–423  
signaling, 350
- reward and pleasure pathways, 22
- reward-discounting tasks, 350



- rimonabant, 160  
 risk. *See also* pre-exposure risk; smoking  
     initiation and progression risk  
     age-specific, measurement of, 35  
     approach-related, 339, 346–349, 362  
     avoidance-related, 339, 351–354, 362  
     control-related, 339, 354–357, 362  
     cumulative, measurement of, 35  
     disease, 541, 550  
     with nicotine dependence, 375–376  
     nicotine metabolism and, 22, 342  
 risk factors  
     adolescent smoking initiation, 211–212, 232,  
         350, 433  
     substance use, 306, 340  
 risk-taking behavior, by adolescents, 195, 199  
 RNA analysis, 142  
 rodent models. *See also* mouse models; rat models;  
     *specific strain*  
     adolescent nicotine exposure, 194–195  
     adolescent sensitivity, 371  
     intravenous self-administration, 410  
     nicotine effects, 368, 435  
     strain-specific differences, 418  
 RSA (respiratory sinus arrhythmia), 361  
 \*RS578776 subunit gene, 43  
 \*RS16969968 subunit gene, 43  
 Russell, M.A.H., 24  
 RVIP (Rapid Visual Information Processing) task,  
     433
- S**
- saccharin, 148, 154, 159  
 S allele, 112, 113  
 sample size/followup  
     in ATBC analysis, 497  
     for developmental trajectory research, 234  
     in TUS-CPS analysis, 498  
 saturated model, 547  
 SBML (Systems Biology Markup Language), 561  
 schizophrenia, 428, 443  
 secondary criteria of nicotine dependence, 76, 77  
 secondary motives scales, 92–93  
 secondary reinforcement, 411, 413  
 secondhand smoke, 20, 246  
 second-stage mixture model, 572  
 self-administration  
     ad libitum (ad lib), 415–416, 419  
     genetic effects on, 146  
     intravenous, 146, 152–157, 410–412  
     oral, 412–413  
     self-control, in children, 344  
     self-insuring firms, 49  
     self-report measures  
         of affect, 446–447  
         components of, 79  
         of craving, 439–440  
         ecological momentary assessment in, 525  
         limitations of, 367  
 SEM. *See* structural equation modeling  
 semi-Bayes approach, 549  
 semistructured paradigms, 524  
 Sensation Seeking Scale, 377  
 sensitivity  
     of measurements, 341  
     modeling, 363–364, 364  
     periodic, 96  
 sensitivity analysis, 570  
 sensory measures, 403  
 Sensory Questionnaire, 423  
 sequential process model, of substance-use  
     comorbidity, 304  
 serotonin  
     association analysis, 268–269  
     genetic variation in, 343  
     metabolism of, monoamine oxidase in, 353  
     regulation of, 540  
     smoking cessation and, 407  
 SES. *See* socioeconomic status  
 seven-point Likert scale, 372  
 shared environment effects  
     in adolescent smoking, 197, 260–261, 264, 280  
     twin studies, 251, 280  
 Shiffman-Jarvik Withdrawal Scale, 440  
 Shiffman Nicotine Dependence Syndrome Scale.  
     *See* Nicotine Dependence Syndrome Scale  
 sibling(s)  
     IBD configurations for, 257–258  
     smoking epochs of, 531  
     as smoking predictors, 523  
     socialization studies, 517  
     twin studies extended to, 251, 262, 279, 280  
 Sibling Partners Study, 526  
 sickle cell discrimination, 47  
 side effects  
     from drinking-water administration, 172  
     from intravenous administration, 146  
 SIFT (Sorting Intolerant From Tolerant)  
     procedure, 554

- simultaneous effect of genes, 32–33
- single-factor dependence, 79n
- single-factor structure, 81
- single-group growth curve model, 219
- single nucleotide polymorphism (SNP)
  - candidate gene variants, 25
  - disease association with, 544
  - genotyping, 43, 257–259
  - nonsynonymous coding, 554
  - as reflection of underlying effects, 546
  - relationships over candidate genes, 545
  - relevance of, 570
  - in whole-genome research, 4
- situational dependence, 27
- six-class solution, example of, 227–228
- skin conductance, 354, 377–378
- skin temperature, 440
- SLC6A3* gene, 198
- SLC6A4* gene, 32, 101, 112, 113
- sleep problems, in children, 357
- slope
  - distribution of, 219
  - factor loading and, 275–276
  - in latent growth curve models, 254, 306, 310
- 129S6 mice, 430
- SMOFAM (Smoking in Families Study), 267
- smoke-free laws, 520
- smoke-free settings, 20, 30, 523
- smokeless tobacco, 147
- smokers, characteristics of, 22
- smoking
  - bans on, 99
  - decline in, 20
  - developmental phenotypes (*See* adolescent developmental trajectories)
  - first experience with (*See* initial sensitivity)
  - frequency of, 369–371, 413, 420
  - during illness, 79, 80
  - nicotine dependence compared with, 87
  - quantitative genetic model and, 512
  - status, 28
  - transition levels, 42–43, 488–490
- smoking cessation
  - age-related changes in, 170
  - barriers to, 4–5, 46
  - CHRNA2* gene in, 407
  - commercial testing, 50
  - comparison groups changes, 493
  - data sets in, 493–494, 494
  - definition of, 492
  - delay discounting factor in, 350
  - demand for, 21
  - difficulties of, 97
  - drugs for, 160
  - failures in, 44–45
  - FTND predictions of, 80
  - future research directions, 454
  - gender differences in, 38
  - heritability in, 406
  - monoamine oxidase decrease during, 351
  - research limitations in, 454–455
  - serotonin pathway and, 407
  - subthreshold pretreatments, 162
  - success predictors, 81, 89, 413, 434
  - symptoms of, 447
  - tailored, 48
- smoking index variable, 30
- Smoking in Families Study (SMOFAM), 267
- smoking initiation, 31, 42
  - adolescent (*See* adolescent smoking initiation)
  - assessment of, age effects in, 279, 322
  - definition of, 29
  - gender differences in, 267
  - linkage analysis of, 267
  - versus* persistence, 406
- smoking initiation and progression risk, 346, 491.
  - See also* pre-exposure risk
  - approach-related, 346–349
  - avoidance-related, 351–353
  - control-related, 354–357
  - endophenotypic measures, 349–351, 353–354, 357–362
  - future research directions, 362–363
- smoking level
  - measurement of, example of, 224–225
  - substance-use comorbidity and, 308, 322
- smoking pattern, factor analysis of, 265
- smoking persistence, 29, 30, 406
  - definition of, 29
  - early-onset smokers' risk for, 200, 212–213, 230–231
- smoking topography devices, 415, 418
- SNP. *See* single nucleotide polymorphism
- social context, 509, 510–511
  - adolescent smoking, 193, 198
  - behavioral genetics in, 514–518
  - future research directions, 527–532
  - proximal measures of, 518–527
  - rationale for, 511–514
  - substance use, 294–295

- social development model, 293  
 socioeconomic status (SES)  
     adolescent smoking and, 232  
     distal to proximal influence, 519–522  
     of hard-core smokers, 35  
     nuanced approaches to, 519–520  
 socioregional influences, 515–516  
 “softening” of smoking, 193  
 software  
     association analysis, 259  
     item response theory, 270  
     linkage analysis, 258  
     ontology, 561, 562  
 Sorting Intolerant From Tolerant (SIFT)  
     procedure, 554  
 SourceForge Web site, 562  
 species-specific responses, 134  
 specific-factor models, of substance use, 306–307,  
     315–316  
 speed congenics, 151  
 spinal cord minipumps, 163  
 spouses, socialization effects from, 517  
 Sprague-Dawley rats, 411, 431, 432–433  
 stage models, developmental trajectories, 233  
 startle-probe measures, 113  
 startle response  
     as affective response, 447–448  
     in humans, 377  
     increases in, 444  
     prepulse inhibition of, 378, 403, 430–432  
     test-retest reliability of, 446–447  
 state laws, against genetic discrimination, 49  
 static clustering, *versus* dynamic clustering,  
     219–220, 232  
 statistics  
     approaches to, 543–550  
     combining genetic studies with, 248  
     developmental phenotypes, 214–231  
     modeling, 248–259, 570  
     ontological knowledge in, 572  
 ST/b inbred mice, 154, 155, 412–413  
 stem cells, 151  
 Sternberg Memory Task, 379, 436–437  
 stigma, nicotine dependence as, 46–47  
 stochastic variable selection  
     hierarchical modeling and, 547–548, 572, 573  
     model selection with, 549–550, 551–552  
 stop-go task, 359  
 strain-specific differences  
     aging, 170  
     conditioned place preference, 158  
     DNA markers, 151  
     five choice serial reaction time task, 432–433  
     genetic, 150  
     mouse models, 153–154, 164–165, 412–413  
     nicotine effects of, 135, 161, 169, 418  
     nicotinic acetylcholine receptors, 172  
     rat models, 411  
     tolerance, 164  
     unraveling of, 142  
 strain surveys, 422  
 stress, 351  
     as influence, 100  
     influences on, 36  
     neuroendocrine response to, 354  
     response mediators, 143  
 Stroop interference task, 379, 440, 451, 452  
 Stroop paradigm, 113  
 structural equation modeling (SEM), 248–249  
     combined with latent class models, 256  
     of developmental trajectories, 215  
     linkage analysis and, 257–258  
     for twin data, 249–257  
 study participants, selection of, 490–492  
 subcutaneous administration, 147, 172  
 subpopulation  
     in latent class analysis, 256  
     in structural equation modeling, 248–249  
 subPSEC (substitution position-specific  
     evolutionary conservation), 554  
 substance use. *See also specific substance*  
     adolescent, shared environmental influences  
         in, 261  
     age-dependent vulnerability to, 195, 198,  
         200–201, 212, 233–234, 292–293  
     attention deficit hyperactivity disorder in,  
         356  
     common-vulnerability model, 291–294, 306,  
         315–316  
     dopamine in, 410, 588  
     early pleasurable use, 374  
     environmental factors influencing, 294–295  
     interpersonal dynamics in, 522  
     Iowa gambling task as predictor, 350  
     modeling of, 43  
     nasal spray non-response, 377  
     novelty seeking in, 292–293, 348–349  
     prevention of, research approaches, 294–295  
     risk factors for, 340  
     specific-factor models, 306–307, 315–316

- substance-use comorbidity, 289–325  
 association between smoking trajectories and, 296–298  
 empirical examples of, 307–323, 496, 502  
 future research directions, 323–324  
 gender differences in, 304  
 gene-environment interactions in, 320  
 importance of studying, 290–292  
 informative phenotypes for, 316–318, 321, 324  
 literature review, 295–296  
 mechanisms underlying, 291–292  
 methodological issues, 321–323  
 modeling, 298–307  
 risk factors, 306  
 two-stage models of, 323
- substance-use disorders  
 common *versus* specific liability to, 292–295  
 diagnosis of, 291  
 shared genetic risk for, 294
- substitution position-specific evolutionary conservation (subPSEC), 554
- subthreshold depression, 352
- sucrose, 154–155, 412
- support interval, 40, 42
- Surgeon General’s Report (1964), 24
- Surgeon General’s Report (1979), 24
- susceptibility loci mapping, 24. *See also* candidate gene studies
- sweat gland activity, 440
- Swedish Twin Registry, 515
- Swiss mice, 435
- Swiss-Webster mice, 158, 161
- switching, between trajectory groups, 255–256
- systems biology, genetic association studies and, 554, 556–559
- Systems Biology Markup Language (SBML), 561
- T**
- targeted treatment, 21–22
- task performance, with nicotine deprivation, 436
- Taste/Sensory Processes subscale, 84
- taxon, nicotine dependence as, 93–94
- team sports, as protective factor, 343
- temperament-based model, 343–344
- test performance, definition of, 75
- test-retest reliability  
 acoustic startle reflex, 446–447  
 ad lib smoking, 415  
 diagnostic tools, 81  
 event-related potential, 429  
 mood effects tests, 375  
 nicotine-dependence measures, 26–27, 29  
 prepulse inhibition startle response, 431
- thapsigargin, 167
- theta rhythm (slow-wave activity), 362
- TH* (tyrosine hydroxylase) gene, 198–199, 269
- threshold  
 factor loading and, 275–276  
 as “smoker,” 42
- time to first cigarette (TTFC)  
 during adolescence, as indicator of adult nicotine dependence, 230–231  
 correlations with, 90  
 factor analysis of, 88–89  
 nicotine metabolism association, 34  
 as physical dependence measure, 79  
 as quitting predictor, 80
- time to maximum tolerance, 162
- tissue levels of nicotine, *versus* plasma levels, 145
- Tobacco Craving Questionnaire, 440
- tobacco dependence, *versus* nicotine dependence, 75
- tobacco industry, 24
- tobacco policies, 7, 20  
 effect on adolescent smoking, 193  
 substance use policies and, 294–295
- tobacco settlement dollars, 4
- tobacco use. *See also* nicotine  
 frequency of, 4, 21, 369–371, 413, 420  
 history of, 27–28  
 smoke compounds, 588
- Tobacco Use Supplement, U.S. Census Bureau’ Current Population Survey (TUS-CPS), 487, 494, 498–500
- tolerance, 162–168  
 genetic effects on, 146  
 to repeated doses, 158
- Tolerance subscale, 90–91
- TPH* gene, 269
- trace fear conditioning, 435
- transcription factor CREB, 160–161, 422
- transcription factor FosB, 161
- transcription levels, alterations in, 40
- transdisciplinary framework, 521
- Transdisciplinary Tobacco Use Research Center (TTURC), 89, 521, 526
- transitional endophenotypes, 107, 108, 200, 233
- translational validation, 172

*TRPC7* gene, 43  
 129T2/SvEmsJ mice, 431  
 TTFC. *See* time to first cigarette  
 TTURC (Transdisciplinary Tobacco Use Research Center), 89, 521, 526  
 TUS-CPS (Tobacco Use Supplement, U.S. Census Bureau's Current Population Survey), 487, 494, 498–500  
 twin studies. *See also specific study*  
     adolescent smoking, 196, 259–262  
     affective regulation, 446–447  
     cross-substance concordance, 317, 319–320  
     *CYP2A6* effect, 40  
     delay aversion, 351  
     ecological momentary assessment, 527  
     epigenetic regulation, 36  
     equal environments assumption in, 516–517  
     event-related potential, 428, 429  
     extended family, 250–252, 262, 279, 280  
     factor analysis, 88–89  
     factor mixture models, 256  
     genomic studies, 589  
     heritability of dependence, 28–29, 86, 342, 406  
     impulsivity, 451  
     limitations of, 279–280  
     multivariate, 252–253, 262–263  
     P300 amplitude, 360  
     prepulse inhibition startle response, 431  
     resting EEG, 426  
     smoking habits, 22, 24  
     smoking initiation, 31  
     structural equation modeling, 249–257  
     substance-use comorbidity, 307–323, 324  
     tobacco use history, 38–39  
     working memory, 437  
 two-factor structure, 81  
 two-stage genetic models, initiation *versus* progression, 323  
 tyrosine hydroxylase (*TH*) gene, 198–199, 269

## U

univariate analysis, substance-use comorbidity, 322  
 unmeasured genetic factors, 4, 511  
 upregulation, of nicotinic receptors, 135, 144–145, 588  
 U.S. Task Force on Community Preventive Services, 4

## V

validity  
     of developmental trajectory research, 234  
     discriminative, 77  
     predictive, 50, 90–91  
 variables  
     independent, 495–496, 498–499  
     observable, 77  
     ontologies to represent knowledge about, 558–559  
     perturbations from, 554  
     in structural equation modeling, 248  
 variance  
     in latent growth curve models, 254  
     partitioning, 270, 280  
 ventral tegmental area (VTA), 152–153, 588  
 verapamil, 167, 168  
 VET (Vietnam Era Twin) Registry, 263–264  
 videotaped paradigms, 524  
 Vietnam Era Twin (VET) Registry, 263–264  
 vigilance, 432–434  
 Virginia 30,000 Study, 262  
 Virginia Twin Registry, 264, 269–279  
     measures, 269–270  
     methods, 270  
     results, 270–276  
     study conclusions, 276–279  
     subjects, 269  
 Virginia Twin Study of Adolescent Behavioral Development, 260  
 visuospatial attention, 434  
 VLMR LR (Vuong-Lo-Mendell-Rubin likelihood ratio) test, 310, 312  
 VTA (ventral tegmental area), 152–153, 588  
 vulnerability  
     of adolescents, 343  
     differences in, 22  
     modeling, 363–364  
     protective factors, 87, 114  
 Vuong-Lo-Mendell-Rubin likelihood ratio (VLMR LR) test, 310, 312

## W

Wald test, 544  
 watershed model, 78–79, 81–82  
 WCST (Wisconsin Card Sorting Test), 378, 436  
 Wechsler Adult Intelligence Test-Revised, 433  
 whole-environment scan, 530

- whole-genome association studies, 4
  - whole-genome linkage scans, 589
  - whole-genome quantitative transcript screening, 170
  - wild-type mice
    - conditioned place preference in, 159, 160, 161, 422
    - in CREB activation studies, 160
    - in nicotine reinforcement, 159
  - WinBUGS, 549
  - Wisconsin Card Sorting Test (WCST), 378, 436
  - Wisconsin Inventory of Smoking Dependence Motives (WISDM), 84–86, 85
    - as assessment tool, 405
    - subscales of, 90–93
  - Wistar rats, 425, 431, 449
  - withdrawal symptoms
    - in adolescents, 192, 194
    - cellular changes, 147
    - environmental influences in, 95
    - heritability of, 30
    - negative affect, 443
    - physical dependence inference from, 77
    - physiology of, 588
    - severity of, 97, 413, 447
    - support interval for, 40
  - within-class variability, estimation of, 220–221, 233
  - working memory, 434–438
  - World Health Organization, 80–81
  - World Mental Health Survey Initiative, 81
- X**
- XSEM (extended structural equation modeling), 249
- Z**
- zygosity, function of, in substance-use phenotypes, 316–317, 320





