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Parsing the Undercontrol/Disinhibition Pathway to Substance Use Disorders: A Multilevel Developmental Problem

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Abstract

A long-standing and diverse body of evidence has documented the importance of externalizing characteristics as very early etiologic predictors of a pathway to severe alcohol and other drug problems and substance use disorder. At the same time, much remains unclear about the mechanistic structure of this pathway, including understanding what the defining characteristics are that encompass the diverse behaviors included in the externalizing domain. This article proposes that the core risk phenotype unifying this domain is behavioral undercontrol/disinhibition. It describes the defining features of this phenotype and outlines the mediators, moderators, and developmental course that characterize the pathway from early risk to a substance use disorder endpoint. A brief summary of the neurocognitive and brain functional response systems that underlie the behavioral phenotype emphasizes the operation of two systems in dynamic tension, one an effortful control system, the other an incentive reactivity system.

Evidence for an Externalizing Pathway

The view that alcoholism--or in modern terminology, alcohol use disorder (AUD)-- is actually a heterogeneous group of disorders has had a long history, but a systematic description of number of types, differentiating characteristics, and developmental course has occurred only within the past quarter century. That work, primarily based on retrospective clinical and epidemiologic survey data, suggested that clinical manifestations, etiology, and prognosis differentiated at least two different "types," one with externalizing comorbid traits and sometimes referred to as "antisocial alcoholism," the other without these traits (Babor et al., 1992; Cloninger, Sigvardsson, & Bohman, 1988; Zucker, 1987). Longitudinal studies in more recent years have been able to prospectively confirm the importance of externalizing characteristics as strong etiologic predictors of the first type (see Zucker, 2006, 2008, for reviews of the older studies as well as of more recent ones).

This longitudinal work has fleshed out a long list of factors associated with the pathway, of this type of AUD, including a high-risk genetic background marked by a positive family history for AUD (Goodwin, Schulsinger, Knop, Mednick, & Guze, 1973); antisocial comorbidity in at least one of the parents (Zucker, Ellis, Fitzgerald, Bingham, & Sanford, 1996); a rearing environment characterized by poor parenting (Olson, Bates, & Bales, 1990; Valiente, Lemery-Chalfant, & Reiser, 2007); exposure to abuse, stress, conflict, and

violence (Hussong et al., 2008; Sanford, Bingham, & Zucker, 1999); low social competence in early childhood (Garnier & Stein, 2002; Pitkänen, Kokko, Lyyra, & Pulkkinen, 2008); involvement with deviant peers (Dielman, Butchart, & Shope, 1993; Dishion, Patterson, Stoolmiller, & Skinner, 1991); and earlier use of alcohol and other drugs (Grant, 1998), with heavier and more problematic use thereafter (Clark et al., 2005; Dubow, Boxer, & Huesmann, 2008; Pitkänen, et al., 2008) and increasing likelihood of moving into early onset AUD or some other drug use disorder (DUD) (Grant & Dawson, 1997, 1998; Hawkins et al., 1997). The robustness of the developmental relationships is indicated by the fact that the great majority of these longitudinal studies began in early or middle childhood, and two have even followed the associations out to the mid-40s.

In this article, we summarize the multidomain evidence for the role of externalizing behaviors in the etiology of substance use disorders (SUDs). The focus is on two issues: (1) the mechanistic structure of the externalizing pathway as a complex multilevel developmental system encompassing behavior, neurocognitive and brain functional response systems, and social environment; and (2) the critical mediators and moderators of developmental course. The discussion of these issues is organized into three sections: (1) the core characteristics of the risk phenotype, (2) the epigenesis of risk and heterogeneity of developmental course, and (3) the probable neurocognitive and brain functional response systems and mechanisms underlying the risk phenotype. Although the majority of work covered pertains to risk for AUD, because of the evidence of a common underlying liability for all disorders of drug involvement (Kendler, Prescott, Myers, & Neale, 2003; Krueger et al., 2002), we have retained the generic SUD terminology when possible.

Core Characteristics of the Externalizing Risk Phenotype for SUD

The heavy research focus on the externalizing behavior cluster has been driven by an interest in identifying the core vulnerability trait, or risk phenotype, that precedes the antisocial behavior and substance abuse associated with adult SUD. To qualify as a candidate for the risk phenotype, the cluster would need to be relatively stable across time and contexts (i.e., it would have traitlike characteristics) and be mechanistically connected to the emergence of the adult characteristics. The externalizing cluster of behaviors in large measure satisfies these criteria. Its content involves both aggressive and delinquent behavior (Achenbach, Howell, Quay, & Connors, 1991; Krueger et al., 2002); the common element is difficulty in control of behavior, not affect. Aggressive behavior includes acts of verbal and physical aggression. Delinquent behavior includes conduct problems such as lying, cheating, stealing, and truancy; that is, it involves rule-breaking and acting in opposition to social norms rather than people. The correlation between the two behaviors in childhood and in adolescence is high ($r \sim 0.7$), reflecting strong but far from perfect overlap (Achenbach & Rescorla, 2003). The externalizing construct is itself a dimensional translation of much of antisocial personality disorder (ASPD) symptomatology, and studies have used both ASPD and SUD symptom measures or diagnoses in combination as an index of the risk phenotype (Kendler, Prescott, Myers, & Neale, 2003; Krueger et al., 2002). At the same time, if difficulty in control of behavior is the critical feature, then the construct descriptor probably should be behavioral undercontrol or behavioral disinhibition.

The issue of labeling is more than a simple dispute about terminology. A careful parsing of these constructs indicates that their subcomponential attributes operate at several levels. Behavioral undercontrol, or behavioral disinhibition, refers to a vulnerability of disinhibitory processes that involves the inability or unwillingness or failure to inhibit behavior even in the face of anticipated or already received negative consequences (Hawkins et al., 1992; Kandel, 1978; Zucker, 2006). Antisocial behavior, delinquency, and rule-breaking fall at the level of observable behavior. However, the construct also subsumes inferential traits like

impulsivity, low behavioral constraint, impaired impulse control, as well as lack of control over cravings for food, sex, or drugs. Undercontrolled individuals are more likely to carry out activities that are normatively inappropriate or socially disapproved, such as aggression or open conflict with authority; they also have greater proneness to engage in risky behaviors without weighing the consequences of their actions. At the same time, this trait is distinct from other, closely related constructs. For example, inhibition is “a temperament or style of reacting with fear or withdrawal when confronted with novelty, including both novel situations as well as unfamiliar adults or peers” (Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Kagan & Snidman, 2004). Inhibition is not the obverse of undercontrol.

For these reasons, although the externalizing label is still being utilized by others, we turn to the finer-grained undercontrol or disinhibition labels, which are more descriptive of the underlying trait (Sher & Trull, 1994; McGue, Iacono, Legrand, Malone, & Elkins, 2001; Wong et al., 2006). From this point on, we refer to the core disinhibitory construct as one of behavioral undercontrol/disinhibition. While it is premature to regard one descriptor as more primary than the other, in order to differentiate them, we use the term *undercontrol* when the referent is to expression at the behavioral level, and the term *disinhibition* when the referent is to the neurophysiological and/or neurocognitive indicator (also see Kagan & Snidman, 2004).

Although the undercontrol/disinhibition characterization makes the best sense, the umbrella it covers is a large one. The jury is still out about whether this will remain the best superordinate characterization, whether the domain should include all of the component pieces described above, and whether such a superordinate level of analysis is most effective for identifying liability. A number of other groups are actively exploring these issues: two (Smith et al., 2007; Dick et al., 2010) are focused on parsing the impulsivity construct, albeit in different ways; a third proposes a composite indicator of neurobehavioral disinhibition that cuts across behavioral, neuropsychological, and affective domains (Tarter et al., 2003); a fourth proposes that the core liability trait is one of behavioral disinhibition, indexed behaviorally by externalizing symptomatology, but also neurophysiologically via brain P300 response (see Iacono & Malone, 2011; Iacono, Malone, & McGue, 2008); a fifth, which proposes that the core liability is one of behavioral undercontrol, delineates a personality structure virtually identical to that in Iacono et al.'s (2008) behavioral disinhibition construct but focuses more on personality structure and genetic basis without elaboration of neurophysiological structure (Slutske et al., 2002); and a sixth, which is closest to our work here, posits a hierarchic structural model involving a behavioral disinhibition higher-order factor superordinate to three lower factors of impulsive sensation-seeking, antisociality/unconventionality, and externalizing symptomatology (see Bogg & Finn, 2010; Wills et al., 2001).

Epigenesis: The Developmental Cascade of Risk, Heterogeneity of Developmental Course, and Possible Indirect Genetic Effects on the Disinhibition Pathway

The brief etiologic summary provided at the beginning of this article enumerates some of the major mediators and moderators of the disinhibitory pathway between early childhood risk and adult disorder. A risk-cumulation additive model would predict that the greater the number of risk factors present, the more likely the SUD endpoint. However, recent work based on long-term, multiwave prospective studies and a dynamic cascade model of risk (cf. Dodge et al., 2009), shows that simple additivity of risk only provides a crude model of risk flow. Timing/sequencing of risk aggregation, density of risk pathway, developmental role demands at outcome, and intermediate risk-offset opportunities are all essential to the

probability of a risky outcome (Dubow et al. 2008; Merline, Jager, & Schulenberg, 2008; Pitkänen et al., 2008).

Another major source of imprecision in characterizing developmental course is driven by the preponderant use of methods of analysis that are variable-centered as opposed to person-centered. If the process of risk development is heterogeneous across the population, then variable-centered analysis will, at best, only crudely characterize intraindividual etiology and developmental course, and, at worst, will provide an erroneous picture. A classic study by Schulenberg and colleagues (Schulenberg, O'Malley, Bachman, Wadsworth, & Johnson, 1996) that utilized data on binge-drinking frequency in a nationally representative sample of college-age youth, illustrates this point. Their trajectory analysis identified six trajectory classes (Never, Rare, Chronic, Decreased, Increased, and "Fling") over the 18-to-24 age interval and showed that the mean trajectory of binge drinking was not reflective of the developmental trajectories of use for *any* of the classes; furthermore, different predictor patterns identified membership in each of the classes. A similar pattern of developmental heterogeneity has been shown for past-year frequency of marijuana use (Schulenberg et al., 2005). Over the past decade, virtually all of the numerous trajectory class studies of adolescent-to-young-adult problem alcohol and marijuana use have found a high-problem class, along with predictors of class membership that clearly differentiate it from one or more of the lower trajectory classes. Studies of early- to middle-adulthood samples have similarly observed this differentiation well into middle adulthood (Jester et al., 2008; Jacob, Bucholz, Sartor, Howell, & Wood, 2005).

In all of this work, predictors of high-trajectory class membership are also the identifiers of the disinhibition/undercontrol pathway: positive SUD family history, parental heavy drinking/AUD, poor parental monitoring and support, early age of onset of alcohol/other drug use, exposure to heavy-drinking peers. The developmentally very early appearance of a high-problem class has also been demonstrated in a trajectory class analysis of disinhibitory behavior over the course of childhood (Jester et al., 2005, 2008). This work, which identified a high disinhibition/disruptive behavior class in a longitudinal study spanning ages 3 to 17 years, not only provides developmental continuity with the older studies; it also indicates very early detectability of the high undercontrol chronic pathway.

The evidence for heterogeneity in the course of undercontrol as a function of gender differences is equivocal. Although differences in level of undercontrol are virtually universally in the stereotypic direction, gender differentiation in causal structure and relationships with other variables is mixed. Differences have sometimes been found in predictive models involving undercontrolled behavior, but degree of effect often varies with age, sometimes disappearing with increasing age over the course of childhood and adolescence (Hussong et al. 2007), and sometimes increasing (Hicks et al., 2007). In other studies, gender differences have either been completely absent or present only in subsidiary parts of the analysis (e.g., Dodge et al., 2009; Slutske et al., 2002). The diversity of these findings suggests that gender differentiation in level of undercontrol does not assure that the relationships among variables will also be different.

Characterizations of the developmental course of undercontrol currently remain heavily focused on continuity and cumulation of risk, not on discontinuity, which would involve transitions from higher to lower risk, or from lower to higher risk, at some point. Change in developmental course that occurs in a nonlinear trajectory--involving acceleration in risk or problem use at one time and/or drop off at another--would be one such example of the phenomenon (see, for example, the Schulenberg et al. [2005] "Fling group" trajectory, which involves both such transitions). Currently the field lacks a framework and a theory to understand these apparent discontinuities in risk level. Statistical characterization of a

curvilinear trajectory or a trajectory with a quadratic component does not meet this criterion because the pathway is in reality continuity of a function with known (or determinable) rate of change. What is missing however, is a conceptual framework that can incorporate exogenous factors not predicted by prior exposure or trajectory vector. Schulenberg and colleagues' concept of developmental discontinuities (Schulenberg, Maggs, & O'Malley, 2003) and disturbances (Zucker, Wong, et al., 2006) is an early effort to incorporate these effects into the system. Discontinuities can create a permanent shift in a trajectory (disturbance as turning point) or, alternatively, can create a "ripple effect" (disturbance as perturbation). The work of Hussong and colleagues (2004, 2008) on developmental snare and launch point effects is another early effort to refine the solely continuity model that has dominated the field.

Potential Sources of Indirect Genetic Effect

Although the body of evidence indicating a mediated trajectory class of disinhibitory risk from early childhood to adult SUD outcome is quite strong, two aspects of these relationships have been largely neglected. One is that many of the risk factors identified as mediators are nested together in the highest-risk families. Thus, families that have the highest probability for transmission of genetic risk (both parents actively alcoholic, at least one with an ASPD diagnosis) are also households where conflict, violence, low educational achievement, parental psychiatric comorbidity, and low socioeconomic status are found (Clark et al., 2004, 2005; Hussong et al., 2007; Loukas, Zucker, Fitzgerald, & Krull, 2003). The other risk factor is that active parent selection of environments takes place not only in marital assortment (Cornelius et al., 2008; Windle, 1997) but even in the selection of neighborhoods where the parents' alcoholic psychopathology is more likely to be sustained (Buu et al., 2007) and where the development of their children's risk is enhanced (Buu et al., 2009). These relationships are all suggestive of substantial gene-environment correlations, that is, genetically influenced individual differences in exposure to risky or protective environments. Moffitt and colleagues (Moffitt, Caspi, & Rutter, 2005) argue that the ideal place to look for G-E interactions is where there is both an environmental main effect and a genetic one. This appears to be the case here, many times over. At the same time, because these interactions are ultimately neurobiological, even though the behavioral risks are statistically correlated does not mean that the interactions are with the same genes, or have sites of action that involve the same neural circuitry. The next section is a beginning effort at specifying what the critical circuitry might be.

Neurocognitive and Brain Functional Response Systems and Their Operational Relationships to the Undercontrol/Disinhibition Developmental Pathway

A thorough developmental systems analysis of the undercontrol/disinhibition pathway requires characterization of bidirectional influences across levels of system ranging from the social contextual to the behavioral, to the neural, to the genetic (Gottlieb, 2003). Fortunately for our purposes here, characterization of cross-system relationships pertaining to the undercontrol/disinhibition domain have been central to the field for some time, and a substantial amount of work, both cross-sectional and developmental, now exists on the linkages between behavior, neurocognition, and brain response. (Studies involving genetic relationships are not covered.)

The neural underpinnings of control and (dis)inhibition involve regions of prefrontal cortex and their extensive circuitries including regions of thalamus, basal ganglia and limbic regions. At least two psychological systems and their likely neural implementation need to be considered (Eisenberg et al., 1997; Nigg, 2000). The systems are in dynamic tension and

modulate each other throughout development. One is an effortful control system (Rothbart & Bates, 1998). *Effortful control* refers to the control of behavior and attention in the service of goals that are distal in time and represented in memory or working memory rather than by immediate incentives and cues. An example would be a child's ignoring a whispering classmate in order to earn some privilege later in the hour. Although executive functioning is a broader construct that encompasses other component abilities, this activity is subsumable in the EF domain. Effortful control involves the ability to regulate behavior to fit contextual demands and maintain a goal set (Miyake et al., 2000, Pennington & Ozonoff, 1996). Effortful control likely reflects activation in prefrontal cortical regions (particularly lateral prefrontal) corresponding with suppression of activity in limbic regions (particularly ventral striatum/nucleus accumbens and possibly amygdala). Although thalamic nuclei, particularly the subthalamic nucleus, also appear to be important, the system can still be regarded heuristically as a "top-down" system.

The second system is an incentive reactivity system; it is relatively automatic in that it does not require mental resources and operates rapidly. It responds to novelty or incentive cues for potential near-term reward or loss by interrupting behavior. Thus, a child may stop talking and actively study a stranger who has entered the room (a cue of novelty or uncertainty; Kagan & Snidman, 2004) or refrain when they see a warning that they are about to lose a privilege (potential loss of reward; Gray & McNaughton, 2000). The incentive reactivity system is distinguishable from primitive appetitive systems such as hunger or fear, which respond to actual reward or loss rather than to simply their signaled potential. The system stimulates high arousal panic or excitement (or freezing) rather than inhibition of previous behavior, and also activates attentional redirection and inspection of the novel stimulus (see Gray & McNaughton, 2000). The appetitive systems are related to the psychobiology of drug response and addiction *after* drug ingestion. Conversely, the incentive reactivity system activates excess incentive cue responding under conditions of experienced failure; thus it is a liability marker for drug problems.

This second construct is very similar to that proposed as reactive control by Eisenberg and colleagues (e.g., Eisenberg & Morris, 2002). It involves suppression of ongoing behavior prompted by signals in the environment rather than by goals in working memory. The neural process is presumed to be subcortical signaling of novelty or potential threat (e.g., from the nucleus accumbens or amygdala), interrupting programs operating in prefrontal cortex. Therefore it is heuristically seen as a "bottom-up" process in brain. When this process fails, undercontrolled behavior occurs and the individual goes forward with the behavior despite a signal of potential problems (see Heitzeg, Nigg, Yau, Zubieta, & Zucker, 2008). Undercontrol may also occur due to overfunctioning of excitement or approach in limbic regions. Although bottom-up, the behavior would functionally appear the same as failure of the top-down system (i.e., failure to modulate excitement for the sake of goals or other less salient contextual demands).

Existing work suggests that top-down and bottom-up responses mutually influence one another (Nigg, 2000; Rothbart & Bates, 2006) both dynamically and developmentally. Thus, incentive response also involves decision-making, but in the context of potential reward or its loss. Imaging studies of healthy adults indicate that the selection of larger later rewards involves dorsolateral prefrontal activation, whereas the selection of smaller, more immediate rewards involves ventral striatum and amygdala activation (Ballard & Knutson, 2009; Hariri et al., 2006; McClure et al., 2004). With drug use, these systems are perturbed by excitation of incentive response circuits, which can overwhelm weakened control functions (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999) and appear phenotypically as behavioral undercontrol (ultimately leading to more drug use).

Developmentally, just when there is major build-up of opportunity for substance use in later adolescence, neural alterations in both frontal “control” system and subcortical “incentive” system are taking place. The dorsolateral prefrontal cortex is one of the last brain regions to mature, with myelogenesis continuing into early adulthood (Benes, 2001; Gogtay et al., 2004). Conversely, limbic and striatal systems are mature and responding to cues during adolescence (Galvan et al., 2006). Overall, the relatively early maturation of subcortical activation systems compared with prefrontal control systems may bias adolescent motivation toward immediate over long-term reward (i.e., disinhibition). How this risk may work during childhood remains to be discovered.

The development of these systems can be perturbed in multiple ways. Early biological insult or genetic risk may interfere with development. Caregiver scaffolding also plays a crucial role in development of both control systems (for reviews, see Eisenberg & Morris, 2002; Nigg, Hinshaw, & Huang-Pollock, 2006; Rothbart & Bates, 1998, 2006). Further, high stress exposure in early development has lasting effects on these brain and neurochemical systems (Braun et al., 2000; Bremner & Vermetten, 2001), as well as increasing the likelihood of substance abuse and externalizing problems in adolescence (Dembo et al., 1988; Harrison et al., 1997). Although much of the work in this area has established only one or another facet of these relationships, recent evidence indicates that insults to these systems are detectable simultaneously in neural activation patterning, behavior, and SUD risk. Heitzeg and colleagues have been able to identify dysregulation of reward-related circuitry as well as prefrontal control in adolescents at high risk for SUD (Heitzeg et al., 2008). Moreover, dysregulation was correlated with externalizing behavior problems. Within the context of high-risk populations, these findings suggest that pre-existing dysregulation of this circuitry from a number of different sources is an early part of the behavioral undercontrol risk pathway. Once substance abuse begins, the system is further perturbed (Heitzeg, Nigg, Yau, Zucker, & Zubieta, in press), presumably leading to further undercontrol.

In summary, there is ample evidence of important development in regulatory abilities and the neural networks that support those abilities during the period from childhood to early adolescence, as well as into early adulthood. Experiential moderators during this period also affect network development. Alcohol consumption in adolescence may also impede development, but current evidence is insufficient to regard this as a firm conclusion. The current behavioral and imaging data also converge in suggesting that frontostriatal-thalamic and limbic networks involved in regulatory control and motivation are also involved in key temperament/personality domains bearing on the development of undercontrol and the regulation of SUD risk. This work strongly suggests that there will be individual differences in neural network functionality between high- and low-undercontrol individuals. This hypothesis needs to be evaluated.

Summary

A convergent network of evidence continues to indicate that one of the core risk pathways to SUD involves a vulnerability to disinhibitory processes. The vulnerability is expressed at the behavioral level by high undercontrol. It is exacerbated by social environmental factors likely to be highly aggregated in high-risk families, and it is regulated at the neural level by two systems, one involving effortful control, largely localized in prefrontal cortical circuitry, and the other involving incentive reactivity, localized in subcortical circuitry. These systems mature at different rates over the course of adolescence and early adulthood; they are also affected by environmental exposure to stress, family conflict, and possibly by precocious alcohol and other drug use. Work to date is suggestive of a considerable synergy across levels of system, and over time for the highest-risk subset of the population. However, the demonstration of such relationships is still in its infancy.

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References

- Achenbach, T.; Rescorla, L. Manual for the ASEBA Adult Forms and Profiles. Burlington, VT: University of Vermont: Research Center for Children, Youth, & Families; 2003.
- Achenbach T, Howell C, Quay H, Conners CK. National survey of problems and competencies among four- to sixteen-year-olds: Parents' reports for normative and clinical samples. *Monographs of the Society for Research in Child Development*. 1991; 56(3):v–120.
- Babor T, Hofmann M, DelBoca F, Hesselbrock V, Meyer RE, Dolinsky Z, Rounsaville B. Type of alcoholics, I: Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Archives of General Psychiatry*. 1992; 49:599–608. [PubMed: 1637250]
- Ballard K, Knutson B. Dissociable neural representations of future reward magnitude and delay during temporal discounting. *Neuroimage*. 2009; 45:143–150. [PubMed: 19071223]
- Benes, FM. The development of prefrontal cortex: The maturation of neurotransmitter systems and their interactions. In: Nelson, C.; Luciana, M., editors. *Handbook of developmental cognitive neuroscience*. Cambridge, MA: MIT Press; 2001. p. 79–92.
- Bogg T, Finn P. A self-regulatory model of behavioral disinhibition in late adolescence: Integrating personality traits, externalizing psychopathology, and cognitive capacity. *Journal of Personality*. 2010; 78:441–470. [PubMed: 20433626]
- Braun K, Lange E, Metzger M, Poeggel G. Maternal separation followed by early social deprivation affects the development of monoaminergic fiber systems in the medial prefrontal cortex of Octodon degus. *Neuroscience*. 2000; 95:309–318. [PubMed: 10619487]
- Bremner JD, Vermetten E. Stress and development: Behavioral and biological consequences. *Developmental Psychopathology*. 2001; 13:473–489.
- Buu A, DiPiazza C, Wang J, Puttler LI, Fitzgerald HE, Zucker RA. Parent, family, and neighborhood effects on the development of child substance use and other psychopathology from preschool to the start of adulthood. *Journal of Studies on Alcohol and Drugs*. 2009; 70(4):489–498. [PubMed: 19515288]
- Buu A, Mansour M, Wang J, Refior SK, Fitzgerald HE, Zucker RA. Alcoholism effects on social migration and neighborhood effects on alcoholism over the course of 12 years. *Alcoholism: Clinical and Experimental Research*. 2007; 31(9):1545–51.
- Clark D, Cornelius J, Wood D, Vanyukov M. Psychopathology risk transmission in children of parents with substance use disorders. *American Journal of Psychiatry*. 2004; 161(4):685–91. [PubMed: 15056515]
- Clark D, Wood D, Martin C, Cornelius J, Lynch K, Shiffman S. Multidimensional assessment of nicotine dependence in adolescents. *Drug and Alcohol Dependence*. 2005; 77(3):235–242. [PubMed: 15734223]
- Cloninger CR, Sigvardsson S, Bohman M. Childhood personality predicts alcohol abuse in young adults. *Alcoholism: Clinical and Experimental Research*. 1988; 12:494–505.
- Cornelius J, Kirisci L, Reynolds M, Homish G, Clark D. Husbands' SUD is associated with higher levels of co-occurring but not non-co-occurring psychiatric disorders among their wives. *Addictive Behaviors*. 2008; 33(9):1231–1234. [PubMed: 18544467]
- Dembo R, Dertke M, Borders S, Washburn M, Schmeidler J. The relationship between physical and sexual abuse and tobacco, alcohol, and illicit drug use among youths in a juvenile detention center. *International Journal of Addictions*. 1988; 23:351–378.
- Dick D. Developmental changes in genetic influences on alcohol use and dependence. *Child Development Perspectives*. 2011 XX, XXX–XXX.
- Dick D, Smith G, Olausson P, Mitchell S, Leeman R, O'Malley S, Sher K. Understanding the construct of impulsivity and its relationship to alcohol use disorders. *Addiction Biology*. 2010; 15:217–226. [PubMed: 20148781]

- Dielman T, Butchart A, Shope J. Structural equation model tests of patterns of family interaction, peer alcohol use, and intrapersonal predictors of adolescent alcohol use and misuse. *Journal of Drug Education*. 1993; 23(3):273–316. [PubMed: 8263671]
- Dishion TJ, Patterson GR, Stoolmiller M, Skinner ML. Family, school, and behavioral antecedents to early adolescent involvement with antisocial peers. *Developmental Psychology*. 1991; 27:172–180.
- Dodge KA, Malone PS, Lansford JE, Miller S, Pettit GS, Bates JE. A dynamic cascade model of the development of substance-use onset. *Monographs of the Society for Research in Child Development*. 2009; 74(3):1–120.
- Dubow E, Boxer P, Huesmann L. Childhood and adolescent predictors of early and middle adulthood alcohol use and problem drinking: The Columbia County Longitudinal Study. *Addiction*. 2008; 103(Suppl. 1):36–47. [PubMed: 18426539]
- Eisenberg N, Morris AS. Children's emotion-related regulation. *Advances in Child Developmental Behavior*. 2002; 30:189–229.
- Eisenberg N, Guthrie I, Fabes R, Reiser M, Murphy B, Holgren R, et al. The relations of regulation and emotionality to resiliency and competent social functioning in elementary school children. *Child Development*. 1997; 68(2):295–311. [PubMed: 9180003]
- Fox N, Henderson H, Marshall P, Nichols K, Ghera M. Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology*. 2005; 56:235–262.
- Galvan A, Hare TA, Parra CE, Penn J, Voss H, Glover G, Casey BJ. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience*. 2006; 26:6885–6892. [PubMed: 16793895]
- Garnier H, Stein J. An 18-year model of family and peer effects on adolescent drug use and delinquency. *Journal of Youth and Adolescence*. 2002; 31:45–56.
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. *The Proceedings of the National Academy of Sciences USA*. 2004; 101:8174–8179.
- Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*. 2002; 159:1642–52. [PubMed: 12359667]
- Goodwin E, Schulsinger F, Knop J, Mednick S, Guze S. Alcohol problems in adoptees raised apart from alcoholic biological parents. *Archives of General Psychiatry*. 1973; 28:238–243. [PubMed: 4684290]
- Gottlieb G. On making behavioral genetics truly developmental. *Human Development*. 2003; 46(6):337–355.
- Grant B. The impact of a family history of alcoholism on the relationship between age at onset of alcohol use and DSM-IV alcohol dependence: Results from the National Longitudinal Alcohol Epidemiologic Survey. *Alcohol Health and Research World*. 1998; 22:144–147. [PubMed: 15706789]
- Grant B, Dawson D. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: Results from the National Longitudinal Alcohol Epidemiologic Survey. *Journal of Substance Abuse*. 1997; 9:103–110. [PubMed: 9494942]
- Grant B, Dawson D. Age at onset of drug use and its association with DSM-IV drug abuse and dependence: Results from the National Longitudinal Alcohol Epidemiologic Survey. *Journal of Substance Abuse*. 1998; 10:163–173. [PubMed: 9854701]
- Gray, JA.; McNaughton, N. *The neuropsychology of anxiety*. 2nd. New York: Oxford University Press; 2000.
- Hariri AR, Brown SM, Williamson DE, Flory JD, de Wit H, Manuck SB. Preference for immediate over delayed rewards is associated with magnitude of ventral striatal activity. *Journal of Neuroscience*. 2006; 26:13213–13217. [PubMed: 17182771]
- Harrison PA, Fulkerson JA, Beebe TJ. Multiple substance use among adolescent physical and sexual abuse victims. *Child Abuse and Neglect*. 1997; 21:529–539. [PubMed: 9192142]

- Hawkins J, Catalano R, Miller J. Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: Implications for substance abuse prevention. *Psychological Bulletin*. 1992; 112:64–105. [PubMed: 1529040]
- Hawkins J, Graham J, Maguin E, Abbott R, Hill K, Catalano R. Exploring the effects of age of alcohol use initiation and psychosocial risk factors on subsequent alcohol misuse. *Journal of Studies on Alcohol*. 1997; 58(3):280–290. [PubMed: 9130220]
- Heitzeg MM, Nigg JT, Yau WY, Zubieta JK, Zucker RA. Affective circuitry and risk for alcoholism in late adolescence: Differences in frontostriatal responses between vulnerable and resilient children of alcoholic parents. *Alcoholism, Clinical and Experimental Research*. 2008; 32:414–426.
- Heitzeg MM, Nigg JT, Yau WY, Zucker RA, Zubieta JK. Striatal dysfunction marks preexisting risk and medial prefrontal dysfunction is related to problem drinking in children of alcoholics. *Biological Psychiatry*. In press.
- Hicks BM, Blonigen DM, Kramer MD, Krueger RF, Patrick CJ, Iacono WG, McGue M. Gender differences and developmental change in externalizing disorders from late adolescence to early adulthood: A longitudinal twin study. *Journal of Abnormal Psychology*. 2007; 116:433–447. [PubMed: 17696699]
- Hussong A, Curran P, Moffitt T, Caspi A, Carrig M. Substance abuse hinders desistance in young adults' antisocial behavior. *Developmental Psychopathology*. 2004; 16(4):1029–1046.
- Hussong AM, Bauer DJ, Huang W, Sher KJ, Chassin LA, Zucker RA. Characterizing the life stressors of children of alcoholic parents. *Journal of Family Psychology*. 2008; 22(6):819–832. [PubMed: 19102603]
- Hussong, AM.; Curran, PJ.; Moffitt, TE.; Caspi, A. Testing turning points using latent growth curve models: Competing models of substance abuse and desistance in young adulthood. In: Cohen, P., editor. *Applied data analytic techniques for turning points research*. New York, NY: Routledge; 2008. p. 81-104.
- Hussong AM, Wirth RJ, Edwards MC, Curran PJ, Chassin LA, Zucker RA. Externalizing symptoms among children of alcoholic parents: Entry points for an antisocial pathway to alcoholism. *Journal of Abnormal Psychology*. 2007; 116(3):529–542. [PubMed: 17696709]
- Iacono WG, Malone SM. Developmental endophenotypes: indexing genetic risk for addiction with the p300 brain event-related potential. *Child Development Perspectives*. 2011 XX, xx-xx.
- Iacono WG, Malone SM, McGue M. Behavioral disinhibition and the development of early-onset addiction: common and specific influences. *Annual Review of Clinical Psychology*. 2008; 4:325–348.
- Jacob T, Bucholz KK, Sartor CE, Howell DN, Wood PK. Drinking trajectories from adolescence to the mid-forties among alcohol dependent males. *Journal of Studies on Alcohol*. 2005; 66(6):745–755. [PubMed: 16459936]
- Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl)*. 1999; 146:373–90. [PubMed: 10550488]
- Jester JM, Nigg JT, Adams KM, Fitzgerald HE, Puttler LI, Wong MM, Zucker RA. Inattention/hyperactivity and aggression from early childhood to adolescence: Heterogeneity of trajectories and differential influence of family environment characteristics. *Development and Psychopathology*. 2005; 17:99–125. [PubMed: 15971762]
- Jester JM, Nigg JT, Buu A, Puttler LI, Glass JM, Heitzeg MM, et al. Zucker RA. Trajectories of childhood aggression and inattention/hyperactivity: Differential effects on substance abuse in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2008; 47(10):1158–1165. [PubMed: 18724257]
- Kagan, J.; Snidman, N. *The long shadow of temperament*. Cambridge, MA: Harvard University Press; 2004.
- Kandel, D. Convergences in prospective longitudinal surveys of drug use in normal populations. In: Kandel, D., editor. *Longitudinal research on drug use*. Washington, DC: Hemisphere; 1978. p. 3-38.

- Kendler K, Prescott C, Myers J, Neale M. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry*. 2003; 60:929–937. [PubMed: 12963675]
- Krueger R, Hicks B, Patrick C, Carlson S, Iacono W, McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: Modeling the externalizing spectrum. *Journal of Abnormal Psychology*. 2002; 111(3):411–424. [PubMed: 12150417]
- Loukas A, Zucker RA, Fitzgerald HE, Krull JL. Developmental trajectories of disruptive behavior problems among sons of alcoholics: Effects of parent psychopathology, family conflict, and child undercontrol. *Journal of Abnormal Psychology*. 2003; 112(1):119–131. [PubMed: 12653420]
- McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate neural systems value immediate and delayed monetary rewards. *Science*. 2004; 306:503–507. [PubMed: 15486304]
- McGue M, Iacono W, Legrand L, Malone S, Elkins I. Origins and consequences of age at first drink: I. Associations with substance-use disorders, disinhibitory behavior, psychopathology, and P3 amplitude. *Alcoholism: Clinical and Experimental Research*. 2001; 25(8):1156–1165.
- Merline A, Jager J, Schulenberg J. Adolescent risk factors for adult alcohol use and abuse: Stability and change of predictive value across early and middle adulthood. *Addiction*. 2008; 103(Suppl. 1): 84–99. [PubMed: 18426542]
- Miyake A, Friedman N, Emerson M, Witzki A, Howerter A. The unity and diversity of executive functions and their contributions to complex ‘frontal lobe’ tasks: A latent variable analysis. *Cognitive Psychology*. 2000; 41(1):49–100. [PubMed: 10945922]
- Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry*. 2005; 62(5):473–481. [PubMed: 15867100]
- Nigg, JT.; Hinshaw, SP.; Huang-Pollack, C. Disorders of attention and impulse regulation. In: Cicchetti, D.; Cohen, D., editors. *Developmental psychopathology*. 2nd. New York: Wiley; 2006. p. 358-403.
- Nigg JT. On inhibition/disinhibition in developmental psychopathology: View from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin*. 2000; 126:220–246. [PubMed: 10748641]
- Olson SL, Bates JE, Bayles K. Early antecedents of childhood impulsivity: The role of parent-child interaction, cognitive competence, and temperament. *Journal of Abnormal Child Psychology*. 1990; 18(3):317–334. [PubMed: 2376656]
- Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry*. 1996; 37:51–87. [PubMed: 8655658]
- Pitkänen T, Kokko K, Lyyra A, Pulkkinen L. A developmental approach to alcohol drinking behavior in adulthood: A follow-up study from age 8 to age 42. *Addiction*. 2008; 103(Suppl. 1):48–68. [PubMed: 18426540]
- Rothbart, MK.; Bates, JE. Temperament. In: Damon, W.; Eisenberg, N., editors. *Handbook of child psychology: Vol. 3. Social, emotional and personality development*. 5th. New York: Wiley; 1998. p. 105-176.(Series Ed.) & (Vol. Ed.)
- Rothbart, MK.; Bates, JE. Temperament in children's development. In: Damon, W.; Lerner, R.; Eisenberg, N., editors. *Handbook of child psychology (Vol 3), Social, Emotional, & Personality Development*. 6th. Hoboken, NJ: Wiley; 2006. p. 99-106.
- Sanford K, Bingham CR, Zucker RA. Validity Issues with the Family Environment Scale: Psychometric Resolution and Research Application with Alcoholic Families. *Psychological Assessment*. 1999; 11(3):315–325.
- Schulenberg J, Merline A, Johnston L, O'Malley P, Bachman J, Laetz V. Trajectories of marijuana use during the transition to adulthood: The big picture based on National Panel data. *Journal of Drug Issues*. 2005; 35:255–279. [PubMed: 16534532]
- Schulenberg J, O'Malley PM, Bachman JG, Wadsworth KN, Johnston LD. Getting drunk and growing up: Trajectories of frequent binge drinking during the transition to early adulthood. *Journal of Studies on Alcohol*. 1996; 57:289–304. [PubMed: 8709588]
- Schulenberg, JE.; Maggs, JL.; O'Malley, PM. How and why the understanding of developmental continuity and discontinuity is important: The sample case of long-term consequences of

- adolescent substance use. In: Mortimer, J.; Shanahan, M., editors. *Handbook of the life course*. New York, NY: Plenum Publishers; 2003. p. 413-436.
- Sher KJ, Trull TJ. Personality and disinhibitory psychopathology: Alcoholism and antisocial personality disorder. *Journal of Abnormal Psychology*. 1994; 103:92-102. [PubMed: 8040486]
- Slutske WS, Heath AC, Madden PA, Bucholz KK, Statham DJ, Martin NG. Personality and the genetic risk for alcohol dependence. *Journal of Abnormal Psychology*. 2002; 111:124-133. [PubMed: 11871377]
- Smith G, Fischer S, Cyders M, Annus A, Spillane N, McCarthy D. On the validity and utility of discriminating among impulsivity-like traits. *Assessment*. 2007; 14:155-170. [PubMed: 17504888]
- Tarter RE, Kirisci L, Mezzich A, Cornelius JR, Pajer K, Vanyukov M, et al. Clark D. Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *American Journal of Psychiatry*. 2003; 160:1078-1085. [PubMed: 12777265]
- Valiente C, Lemery-Chalfant K, Reiser M. Pathways to problem behaviors: Chaotic homes, parent and child effortful control, and parenting. *Social Development*. 2007; 16:249-267.
- Wills TA, Cleary S, Filer M, Shinar O, Mariani J, Spera K. Temperament related to early onset substance use: Test of a developmental model. *Prevention Science*. 2001; 2:145-163. [PubMed: 11678291]
- Windle M. Mate similarity, heavy substance use and family history of problem drinking among young adult women. *Journal of Studies on Alcohol*. 1997; 58:573-80. [PubMed: 9391916]
- Wong MM, Nigg JT, Puttler LI, Fitzgerald HE, Jester JM, Glass JM, et al. Zucker RA. Behavioral control and resiliency in the onset of alcohol and illicit drug use: A prospective study from preschool to adolescence. *Child Development*. 2006; 77(4):1016-1033. [PubMed: 16942503]
- Zucker, RA. The four alcoholisms: A developmental account of the etiologic process. In: Rivers, PC., editor. *Alcohol and Addictive Behaviors Nebraska Symposium on Motivation 1986*, 34; Lincoln, NE: University of Nebraska Press; 1987. p. 27-83.
- Zucker, RA. Alcohol use and the alcohol use disorders: A developmental-biopsychosocial systems formulation covering the life course. In: Cicchetti, D.; Cohen, DJ., editors. *Developmental psychopathology: Vol. 3. Risk, disorder and adaptation*. 2nd. New York, NY: Wiley; 2006. p. 620-656.
- Zucker RA. Anticipating problem alcohol use developmentally from childhood into middle adulthood: What have we learned? *Addiction*. 2008; 103(Suppl. 1):100-108. [PubMed: 18426543]
- Zucker RA, Ellis DE, Fitzgerald HE, Bingham CR, Sanford KP. Other evidence for at least two alcoholisms, II: Life course variation in antisociality and heterogeneity of alcoholic outcome. *Development and Psychopathology*. 1996; 8(4):831-848.
- Zucker RA, Wong MM, Clark DB, Leonard KE, Schulenberg JE, Cornelius JR, Puttler LI. Predicting risky drinking outcomes longitudinally: What kind of advance notice can we get? *Alcoholism: Clinical and Experimental Research*. 2006; 30(2):243-252.