Substance Use Disorders as Externalizing Outcomes

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Abstract

This chapter discusses substance use disorders (SUDs) as externalizing outcomes while also touching on psychopathy. It begins by reviewing available evidence regarding general dispositional vulnerability to SUDs and conditions involving impulsivity and antisocial behavior. It then considers brain systems implicated in inhibitory control and reward-seeking behavior, along with their relationship to substance use problems. It also describes an empirically based organizing framework, the externalizing spectrum model, for identifying similarities and differences among externalizing outcomes in terms of symptomatic features and causal origins. It explores the psychological and neurobiological mechanisms underlying general vulnerability to externalizing problems, as well as the factors that influence this vulnerability in the direction of SUDs compared to other outcomes. The chapter concludes with an assessment of some relevant unresolved questions and directions for future research.

Key Words: substance use disorders, externalizing outcomes, psychopathy, impulsivity, antisocial behavior, brain systems, inhibitory control, reward-seeking behavior, externalizing spectrum model

I went looking for trouble, and I found it.
—Charles Ponzi (1934)

We wants it, we needs it. Must have the precious . . .
—Gollum (2002)

As discussed elsewhere in this volume, considerable evidence suggests that impulse control (externalizing) problems of differing types co-occur frequently and that this comorbidity is attributable to common dispositional tendencies. However, despite this overlap, different externalizing conditions can and do present as quite distinct from one another, and individuals with matching diagnoses can exhibit their pathologies in markedly contrasting ways. Two externalizing conditions that may appear strikingly different—although they co-occur at levels well above chance—are psychopathy and substance abuse. This chapter focuses in particular on substance use disorders (SUDs) as externalizing outcomes while also providing some perspective on psychopathy. We describe an empirically based organizing framework, the externalizing spectrum model, for discerning commonalities versus distinctions among externalizing outcomes—both in terms of symptomatic features and causal origins. We review what is known about brain systems relevant to inhibitory control (see also Corr & McNaughton, this volume) and reward-seeking behavior (see also Zisner & Beauchaine, this volume), and we discuss the interplay between these systems vis-à-vis substance use problems. We consider the question of what a general vulnerability to externalizing problems might entail, psychologically and neurobiologically, and what influences shape this vulnerability in the direction of SUDs compared to other outcomes. We conclude with a discussion of key unanswered questions and suggested avenues for future research.
Dispositional Liability for Substance Problems

Problems with alcohol and illicit drugs run in families, and genes are known to play an important role in intergenerational transmission of SUDs. Current etiological models of SUDs provide compelling evidence for generalized heritable liability toward experimentation with substances of differing types and subsequent development of SUDs, as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). Regarding illicit drugs, results from twin studies indicate that a common heritable factor contributes to usage and problems with multiple classes of illicit substances (cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates) rather than specific genetic factors accounting for problems with each class of substance (Kendler, Jacobson, Prescott, & Neale, 2003a). Furthermore, considerable evidence exists that the heritable factor that accounts for problems with illicit drugs of differing types also contributes to problematic use of alcohol (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Krueger et al., 2002) and nicotine (Han, McGue, & Iacono, 1999; Hicks et al., 2007)—although some evidence also exists for more specific genetic influences (i.e., apart from the general factor) on problems with alcohol versus illicit drugs (Kendler, Prescott, Myers, & Neale, 2003b). Taken together, research on the etiological bases of SUDs points to a common heritable factor.

Of course, twin studies tell us nothing about the pathophysiology of SUDs and other externalizing behaviors. Thus, questions emerge regarding precisely what is inherited that confers vulnerability to SUDs. As discussed in detail in other chapters of this volume (e.g., Corr & McNaughton, this volume; Zisner & Beauchaine, this volume), this broad liability appears to involve impairment in the capacity for inhibitory control (“disinhibition”) or perhaps proclivities that operate against the pathophysiology of SUDs and other externalizing problems, including childhood disruptive behavior disorders (conconduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder; e.g., Burt, Krueger, McGue, & Iacono, 2001; Young, Stallings, Corley, Krauter, & Hewitt, 2000; Young et al., 2009) and adult antisocial behavior (Hicks et al., 2004; Krueger et al., 2002; Malone, Taylor, Marmorstein, McGue, & Iacono, 2004). Although this highly heritable (Krueger et al., 2002; Young et al., 2000) vulnerability confers broad risk for externalizing problems, its specific behavioral expression (e.g., as dependence on one substance vs. another or persistent aggressive deviance) is determined substantially by environmental influences (Kendler et al., 2003b; Krueger et al., 2002; see also Beauchaine & McNulty, 2013; Beauchaine, McNulty, & Hinshaw, this volume). Notably, some evidence suggests that heritable disinhibitory liability also contributes modestly to the occurrence of certain internalizing problems as well (those involving anhedonia, dysphoria, and distress in particular; see e.g., Kendler et al., 2003b; see also Nelson, Strickland, Krueger, Arbisi, & Patrick, 2015; Sauder, Derbidge, & Beauchaine, in press; Vaidyanathan, Patrick, & Iacono, 2011).

Consistent with the idea of a general dispositional vulnerability to SUDs and conditions involving impulsivity and antisocial behavior, problems of these types also show common personality correlates. Investigators in this area (e.g., Sher & Trull, 1994) have identified two trait domains as particularly relevant: disinconstraint, which encompasses traits such as impulsivity, sensation seeking, and unconventionality; and negative affectivity, which encompasses traits such as anxiety, suspiciousness, and aggressiveness. In the three-factor model of personality embodied in Tellegen’s (Tellegen & Waller, 2008) Multidimensional Personality Questionnaire (MPQ), these two broad domains are represented by higher order factors of Constraint (reversed) and Negative Emotionality (NEM). Prior research has demonstrated relations between these MPQ factors and externalizing conditions of various types including SUDs, along with child and adult antisocial behavior (e.g., Krueger, Caspi, Moffitt, Silva, & McGee, 1996). Furthermore, Krueger (1999) reported that scores on the NEM and CON factors of the MPQ at age 18 predict subsequent diagnoses of antisocial personality disorder (APD) and substance dependence at age 21.

Thus, available evidence supports an integrative perspective on externalizing problems and tendencies in which antisocial behaviors and substance-related disorders (or partial symptomatic expressions thereof), along with the personality traits disinconstraint/impulsivity and negative emotionality, indicate a largely heritable common liability factor. In the next section, we describe a comprehensive model of problems and traits in this domain (the externalizing spectrum model) that provides a useful point of reference for thinking about alternative behavioral expressions of...
disinhibitory liability (e.g., in the form of SUDs vs. other problems).

The Externalizing Spectrum Model

Krueger et al. (2007) formulated a measurement model of externalizing conduct, the self-report externalizing spectrum inventory (ESI). Building upon earlier work by Krueger et al. (2002) and others (Kendler et al., 2003; Young et al., 2000), these investigators undertook a fine-grained analysis of disinhibitory behaviors and traits in order to delineate more clearly the scope and structure of the externalizing spectrum. They began by identifying various constructs embodied in DSM definitions of externalizing disorders included in the Krueger et al. (2002) analysis, and they then developed questionnaire items to indicate these constructs. They also surveyed the literature to identify other behavioral and trait constructs linked conceptually or empirically to the externalizing dimension and developed items to index these constructs. Over three iterative rounds of data collection and analysis (using item response modeling and factor analytic techniques) with a total of 1,787 participants, the authors refined the overall item set to clarify the nature of constructs associated with the broad externalizing factor and arrived at a final array of constructs, each operationalized by a unique subscale.

The resultant inventory, the ESI, consists of 415 items organized into 23 unidimensional subscales reflecting content domains of impulsiveness/sensation-seeking, irresponsibility/externalization of blame, aggression, deceitfulness, and substance use/problems of differing types. The subscales of the ESI exhibit a bifactor structure: all 23 scales load on a general factor labeled externalizing (Krueger et al., 2007) or disinhibition (Patrick, Kramer, Krueger, & Markon, 2013a), with certain scales also loading on one of two subsidiary factors. Scales that index recreational and problematic use of alcohol, marijuana, and other drugs load together on a subsidiary substance abuse (Patrick et al., 2013a) or addiction proneness (Krueger et al., 2007) factor. Another set of scales—those indexing relational aggression and deficient empathy, along with destructiveness, excitement seeking, rebelliousness, and dishonesty—load together on a separate callous-aggression subfactor (Patrick et al., 2013a). A schematic depiction of the ESI measurement model is presented in Figure 3.1. A brief (160-item) form of the ESI was developed by Patrick et al. (2013a) to provide for more efficient assessment of both the lower order facets of the model (through shorter length content scales) and the higher order factors (through item-based scales indexing the ESI’s general factor and two subfactors).

Some aspects of this model warrant specific attention. First, the emergence of distinctive subfactors within the ESI model is attributable to the fact that many more indicator variables, which capture

Figure 3.1  Schematic depiction of best-fitting confirmatory bifactor model of the Externalizing Spectrum Inventory (ESI; Krueger et al., 2007; Patrick et al., 2013a). The model is represented schematically because the 23 subscales of the ESI included in the model are too numerous to depict in full. Subscripted “S” denote differing subscales. Some of the ESI subscales (those labeled in black, including irresponsibility, problematic impulsivity, theft, impatient urgency, planful control [−], dependability [−], and alienation) load exclusively on the general externalizing (disinhibition) factor. Other subscales, in addition to loading on the general externalizing factor, also load on either the callous-aggression subfactor (those labeled in red, including relational aggression, empathy [−], destructive aggression, excitement seeking, physical aggression, rebelliousness, and honesty [−]) or the substance abuse subfactor (those labeled in blue, including marijuana use, drug use, marijuana problems, alcohol use, drug problems, and alcohol problems).
more nuanced expressions of externalizing prone-ness, were included in comparison with previous models focused on fewer (mostly disorder-related) indicators (Kendler et al., 2003b; Krueger et al., 2002; Young et al., 2000). Krueger et al. (2007) interpreted these subfactors as indicative of broad thematic trends in the expression of externalizing liability—i.e., toward aggressive-exploitative behavior on one hand, and hedonistic self-medication on the other—which may reflect shaping effects of other etiological influences on general externalizing liability. Possibilities along these lines are considered further later.

A second and related point is that the general factor of the ESI model, although presumably quite similar to factors of earlier externalizing models, is probably not identical. One reason is that the ESI is entirely self-report based, whereas earlier models included symptom variables assessed through diagnostic interview (for a discussion of method variance effects in externalizing assessment, see Blonigen et al., 2010). Another reason is that the ESI general factor is parameterized to be independent of the model’s two subfactors by partitioning covariance among content subscales into that associated with the general factor versus (in the case of subscales containing variance separate from this and reflecting either callous-aggressive tendencies or substance abuse) one or the other subfactor. As a consequence, the general factor is defined most strongly by scale measures indexing broad behavioral proclivities toward irresponsibility and problematic impulsivity in particular (with loadings above .9). Scales tapping narrower dispositional or behavioral tendencies, including most of those associated with the ESI’s two subfactors, callous-aggression and substance use, load to lesser degrees (.45–.79). The notable exceptions are scales that assess tendencies toward theft, fraudulence, and drug problems, which load only slightly lower on the general factor (i.e., .87 in each case).

One further point of note is that the subfactors of the ESI model, although parameterized to be independent of the general factor, are in fact defined by residual variances in scales that load as well on the general factor. Thus, although the factors are independent of each other within the ESI bifactor model, the scales that demarcate the factors are all correlated. Work directed at identifying indicators of one or the other ESI subfactor that covary minimally with the ESI general factor would, if successful, support the presence of distinct influences contributing to contrasting expressions of disinhibitory liability and help to clarify the psychological nature of these influences. Work of this kind will likely need to consider variables from domains other than self- or interview-based report (e.g., behavioral, biological) and make use of longitudinal-developmental designs (cf. Patrick & Drislane, 2014).

**Neurobiological Systems Relevant to Trait Disinhibition and Substance Abuse**

This section considers brain systems implicated in control of behavioral tendencies and down-regulation of emotional responses and systems theorized to mediate reactivity to pleasurable events and cues signaling the possibility of reward. Following this discussion, we proceed with another major section focusing on the externalizing spectrum model and its implications for differing outcomes associated with disinhibitory liability.

**Brain Circuitry for Inhibitory Control**

At the most basic level, priming of defensive or appetitive motivational behavior can arise through exposure to simple conditioned stimuli in the environment that automatically activate the amygdala or the midbrain (mesolimbic) dopamine (DA) system. For example, LeDoux (1995, 2000) described a “quick and dirty” processing pathway from the sensory thalamus to the lateral nucleus of the amygdala along which simple acoustic information can be transmitted; because of the existence of this pathway, fear activation can occur to a conditioned tone (CS) even following massive destruction of the neocortex. A similar fast processing pathway appears to exist for the visual system, involving the basolateral nucleus of the amygdala (Davis & Lee, 1998); this pathway has been the focus of human research on “unconscious” processing of visual fear cues including faces (Whalen et al., 1998) and phobic objects (Öhman, 1993). Berridge and Robinson (1998) likewise characterized the mesolimbic dopamine system has having a low-level, implicit processing capacity, whereby simple cues in the environment can instigate appetitive mobilization (“wanting”) in the absence of “conscious” awareness.

Importantly, however, both the amygdala and midbrain DA systems exhibit extensive neural connectivity with various regions of the neocortex. These connections afford mechanisms through which higher brain processes (e.g., memories, images, plans) can influence processing and reactivity to emotional events, and emotional reactions can in turn influence these higher brain processes.
Especially important in the present context are connections between these subcortical motivation/affect systems and the prefrontal cortex (PFC). The existence of these connections leads to the question: What specific functional role does the PFC play in affective-motivational processing?

In general, the PFC is thought to be crucial for “top-down” processing; that is, the guidance of behavior by internal representations of goals or states (Miller & Cohen, 2001). The PFC is the region of neocortex that is most highly evolved in primates, and it is believed to account for the diversity and flexibility of behavioral strategies exhibited by humans. A number of investigators have proposed that the PFC is especially important for coping with novel or dynamic situations in which selection of appropriate behavioral responses needs to be made on the basis of internal representations of goals and strategies rather than immediate stimulus cues alone (e.g., Cohen & Servan-Schreiber, 1992; Miller, 1999; Wise, Murray, & Gerfen, 1996). Miller and Cohen (2001) proposed an elegant, integrative model in which the control functions of the PFC arise from its specialized capacity for online maintenance of goal representations: by maintaining patterns of activation corresponding to goals and the means needed to achieve them, the PFC provides biasing signals to other regions of the brain with which it connects. These signals serve to prime sensory-attentional, associative, and motor processes that support the performance of a designated task by directing activity along relevant brain pathways. An appealing feature is that this model provides a mechanistic account of PFC function that avoids the circularity of mentalistic (i.e., PFC as “executive”) accounts.

The major focus of Miller and Cohen’s (2001) model was on cognitive control functions (i.e., guidance of behavior on the basis of internal representations) associated with the dorsolateral PFC. This subdivision of the PFC plays a critical role in working memory processes, involving the maintenance of a discrete stimulus representation across a temporal delay (Goldman-Rakic, 1996). For example, in humans, performance of a working memory task that involves matching current stimuli to earlier stimuli in an ongoing stream (the “n-back” task; Cohen et al., 1994) preferentially activates the dorsolateral PFC, with the degree of activation increasing as a function of memory load (Cohen, 1997). The dorsolateral PFC is also distinguished by its close connections with sensory association cortices (including occipital, temporal, and parietal); its prominent projections to premotor areas in the medial and lateral frontal lobes, as well other motor structures including the basal ganglia, the cerebellum, and the frontal eye fields; and its ability to encode relations between stimulus events and thus represent rules (mappings) required to perform complex tasks (Roberts, Robins, & Weisskrantz, 1998). As a function of these capacities, this region also plays a role in more active processes associated with inhibition and regulation of behavioral responses (cf. Petrides, 2000). For example, the control function of the dorsolateral PFC is important for performance on the Stroop color-naming task (MacDonald, Cohen, Stenger, & Carter, 2000) and for performance of the visual antisaccade task, which entails active inhibition and redirection of reflexive eye movements (Broere, Crawford, & den Boer, 2001; Müri et al., 1998).

A further, and intriguing, element in the Miller and Cohen (2001) cognitive control model of PFC function is the role ascribed to DA neuron activity. Recognizing that patterns of PFC activity contributing to attainment of a goal (i.e., biasing other brain systems to respond in goal-relevant ways) must be reinforced in order to recur under appropriate circumstances in the future, the suggestion is that this reinforcing function may be served by dopaminergic projections to the PFC from the midbrain DA system, as well as by DA neurons within the PFC itself. Here, the reward prediction error or “incentive salience” function of DA (see later discussion) serves to strengthen connections between neurons that signal expectation of reward and representations in the PFC that guide the actions required to achieve the reward. In other words, the mesocorticolimbic DA activity supplies the incentive for appropriate PFC representations to recur in a task context in which those representations have previously facilitated goal attainment. With regard to pathologic function, Montague, Hyman, and Cohen (2004) proposed—in line with Robinson and Berridge (2000)—that the normal role of the DA system as a facilitator of complex, PFC-mediated behavior (such as that required to function in a complex work environment or obtain a college degree) can be “hijacked” by drugs of abuse that sensitize the system and direct its activity toward ritualized, maladaptive action patterns (see also Zisner & Beauchaine, this volume). From this perspective, it is reasonable to think that deficits in PFC function that arise from genetic and/or experiential factors could render an individual especially vulnerable to this sort of hijacking (i.e., because of a...
lack of incentive to engage in activities that do not lead to immediate, tangible rewards).

Lesser attention was devoted in Miller and Cohen’s (2001) model of the ventromedial and orbitofrontal regions of the PFC, which have collectively been termed the orbitomedial PFC (e.g., Blumer & Benson, 1975). These regions connect more directly and extensively than the dorsolateral PFC with medial temporal limbic structures including the amygdala, hippocampus and associated neocortex, and hypothalamus. As a function of these limbic connections, the orbitomedial PFC appears to play a more dominant role in the anticipation of affective consequences of behavior (Bechara, Damasio, Tranel, & Damasio, 1997; Wager & Thagard, 2004) and in the unlearning of stimulus-reward associations (i.e., reversal learning; Dias, Robbins, & Roberts, 1996; Rolls, 2000). Both the dorsolateral and orbitomedial divisions of the PFC are themselves richly interconnected, so their functions need to be viewed as interdependent. Nevertheless, Bechara, Damasio, Tranel, and Anderson (1998) reported that patients with dorsolateral PFC lesions showed impairments on a working memory tasks but not on a gambling task involving affect-guided decision making, whereas the reverse was true of patients with ventromedial PFC lesions.

Particular research attention has been devoted in recent years to another key function of the orbitomedial PFC—namely, its role in regulating emotional reactivity and expression. It has long been known that lesions of this brain region are associated with dramatic increases in impulsive, irresponsible, and aggressive behavior. The best known example of this is the railway worker Phineas Gage, who in 1848 suffered an accident in which an iron tamping rod was driven through his skull from the base to the top, causing extensive damage to the PFC—in particular, the orbitomedial region (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Prior to the accident, Gage was described as capable, dependable, and courteous, whereas after he was characterized as impulsive, stubborn, antagonistic, and reckless. This constellation of features arising from damage to the orbitomedial PFC has been labeled “acquired sociopathy” (Damasio, Tranel, & Damasio, 1990). Other more recent cases of this type have been reported on by Anderson, Bechara, Damasio, Tranel, and Damasio (1999) and Blair and Cipolotti (2000). Impulsive aggressive behavior was identified as a prominent feature in each.

Davidson, Putnam, and Larson (2000) proposed that the orbitomedial PFC functions to suppress emotional activation elicited automatically by cues for reward or punishment. These authors further suggested that deficits in the ability to regulate negative affect associated with orbitomedial PFC impairment may be an important factor underlying impulsive, angry aggression among some individuals. Miller and Cohen (2001) conceptualized this affect suppression function of the orbitomedial PFC in terms of the general biasing function: the orbitomedial PFC, with its direct connections to limbic structures, operates to bias task-relevant processes against competition from “hot” (motivationally charged) processes arising in social or emotional contexts. Consistent with this perspective, human neuroimaging studies provide evidence that the orbitomedial PFC is selectively activated during efforts to suppress affect evoked by positive or negative emotional stimuli (Beauregard, Levesque, & Bourgouin, 2001; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004). Human and animal studies also support a role for the orbitomedial PFC in the extinction of fear (e.g., Phelps, Delgado, Nearing, & LeDoux, 2004; Quirk, Russo, Barron, & Lebron, 2000), an active process of relearning rather than a passive process of forgetting (LeDoux, 1995, 2000).

Two other important brain regions for regulating emotional behavior are the hippocampus and the anterior cingulate cortex (ACC). The hippocampus connects with the amygdala and midbrain DA system as well as the PFC and appears to be important for linking affective responses and goals to complex configural stimuli (contexts). Thus, lesions of the hippocampus block acquisition of contextual fear conditioning, but not simple cue conditioning (LeDoux, 1995). Regarding the PFC, Cohen and O’Reilly (1996) postulated that its connections with the hippocampus provide a mechanism through which goal representations can be activated dynamically by contextual cues in the environment to guide complex, delayed action sequences (e.g., stopping by the store at the end of the day to pick up groceries needed for dinner). Impairments in hippocampal function would be expected to contribute to a simpler, explicit, cue-driven style of affective processing. On the other hand, the ACC, which connects with premotor and supplementary motor regions as well as with limbic structures (including amygdala and hippocampus) and the PFC, has been conceptualized as a system that invokes control functions.

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of the PFC as required to perform a task successfully by detecting errors in performance as they occur (Scheffers, Coles, Bernstein, Gehring, & Donchin, 1996), by monitoring conflict arising from activation of competing response tendencies (Carter et al., 1998), or by estimating the likelihood of committing an error at the time a response is called for (Brown & Braver, 2005). Impairments in ACC function would be expected to interfere with the ability to inhibit prepotent behavioral responses and to avoid repetition of errors.

**Brain Circuits for Reward and Incentive Salience**

It has long been known that the mesolimbic DA system, including DA neurons in the ventral tegmental area and their projections to structures including the nucleus accumbens, as well as the mesocortical DA system, including DA neurons in the ACC, PFC, and other regions of the forebrain, play crucial roles in reward processing and reward-related behavior (see Zisner & Beauchaine, this volume). The mesolimbic (midbrain) dopamine system has been emphasized in particular as playing a crucial role in addictive behaviors. The prevailing perspective for many years was that this system mediates the hedonic value (pleasurable) component of incentives (e.g., Olds, 1956; Olds & Milner, 1954; Phillips, 1984; Shizgal, 1999; Wise, 1985). However, this view was challenged in the 1990s by single-cell recording studies demonstrating that DA neurons of the ventral tegmental area and substantia nigra in monkeys respond primarily to events that predict reward rather than to rewards themselves (Schultz, 1998; Schultz, Apicella, & Ljunberg, 1993). For example, in appetitive conditioning paradigms entailing delivery of a food rewards following light cues, DA cells in these brain regions show increased firing upon occurrence of the reward itself—but only on initial learning trials when the reward is unexpected (i.e., not predicted). As animals learn contingencies between reward cues (light) and reward delivery (food), DA firing propagates backward from reward delivery to cue presentation. Additionally, once learning is established, (a) DA neurons exhibit a decrease below their tonic rate of firing on occasions when the food reward is withheld following light cues, and (b) neuronal firing is observed during reward presentation itself if such presentation occurs at a time other than after the light cue (i.e., when the reward is unexpected).

A key conclusion is that neurons in the midbrain (mesolimbic) DA system code for “prediction error”—that is, the degree to which a reward stimulus or a cue for reward is unexpected (Montague, Dayan, & Sejnowski, 1996; Schultz, 1998). In the appetitive conditioning paradigm just described, neuronal firing shifted from the reward to the light CS because the timing of the reward became predictable, whereas the occurrence of the CS remained unpredictable. By extension, the midbrain DA system may not be involved so much in coding the hedonic (pleasurable affective) value of reward, but in the process of learning to connect rewards to cues in the environment and thus in recognition of opportunities for reward and in the sequencing of goal-directed actions.

An extension of this view of the role of the midbrain DA system in reward processing was put forth by Berridge and colleagues (e.g., Berridge & Robinson, 1998; Berridge, Venier, & Robinson, 1989). These investigators proposed that neurons in the mesolimbic DA system mediate the *incentive salience* of rewards, as opposed to their hedonic value (pleasurableness). A key concept in this model is the distinction between “wanting” and “liking.” “Wanting” entails attentional saliency accompanied by an active inclination to pursue, whereas “liking” refers to the pleasure derived from consuming a reward; both processes are posited to include a core implicit element, such that “wanting” or “liking” can be instigated in the absence of conscious awareness. Berridge and colleagues proposed that dopaminergic neurons in the mesolimbic system are critical for the “wanting” component of reward (i.e., the attribution of incentive salience to rewards and reward cues, such that they become objects of desire to be actively pursued), but not for the “liking” component (registering the hedonic impact of reward stimuli). A foundation for this viewpoint was work demonstrating that neurotoxic destruction of neurons in key regions of the midbrain DA system (nucleus accumbens, neostriatum) eliminate food-seeking behavior in rats without affecting facial indicators of hedonic responses to the food itself (cf. Berridge & Robinson, 1998). Thus, damage to the midbrain DA system diminishes “wanting” of rewards (i.e., they are no longer desired, attended to, and actively pursued) without affecting “liking” (i.e., rewards, when administered, are still “enjoyed”). Other work by these investigators suggests that the hedonic (“liking”) component of reward is mediated by other interconnected structures within the basal forebrain...
and hindbrain—including the opioid receptor-rich shell of the nucleus accumbens, the ventral pallidum, and the brainstem parabrachial nucleus (cf. Berridge, 2003).

A key point of divergence between the “prediction error” model of Schultz and colleagues and the incentive salience model set forth by Berridge and Robinson is that the former model implies an essential role for DA in reward learning. Berridge and Robinson (1998) cast doubt on this role by presenting evidence that rats with extensive neurotoxin-induced DA depletion still show attention and enhancement of hedonic reactivity to a rewarding stimulus, respectively, after a stimulus is paired with a nausea-inducing agent (lithium chloride) or a palatability-enhancing agent (diazepam). However, McClure, Daw, and Montague (2003) subsequently proposed an alternative reward-learning model (the “actor-critic” model) that reconciles the prediction error position with the incentive salience model. Here, the reward-prediction error coded by DA neural activity serves the dual purpose of imbuing relevant stimuli with incentive value and biasing action selection so as to maximize reward outcomes (see also Gatzke-Kopp & Beauchaine, 2007). The incentive salience model set forth by Berridge and colleagues served, in turn, as the foundation for an influential model of processes underlying drug addiction: the incentive sensitization model (Berridge & Robinson, 1995; Robinson & Berridge, 1993, 2003). The central idea is that repeated ingestion of drugs causes the midbrain DA system to become sensitized to drug cues. Once established, this sensitization is extremely persistent. Evidence for enduring changes in this system as a function of drug taking includes animal data showing increased effects of stimulant drugs on psychomotor activation and accompanying morphologic changes in DA neurons with repeated use and human neuroimaging findings showing that the midbrain DA system is activated strongly when those addicted to substances are exposed to drug-associated stimuli—and when they receive the drug (cf. Robinson & Berridge, 2000; Volkow, Fowler, & Wang, 2004; Volkow, Wang, Fowler, & Tomasi, 2012). According to the incentive sensitization model, the idea that “wanting,” mediated by striatal DA neurons, is sensitized by repeated drug taking (and potentially by other forms of addictive behavior) helps to explain the inordinate salience that drug cues have for addicts and their compulsion to find their drug of choice (i.e., craving = “wanting”). The model also accounts for why addicts persist in seeking and ingesting drugs even after the pleasure achieved by taking the drug has waned and aversive consequences accrue. Individual differences are presumed to exist in susceptibility of the “wanting” system to sensitization as a function of variables such as genes, sex-related hormones, and experience (Robinson & Berridge, 2000).

In sum, neuroscientific research indicates that the midbrain DA system is integral to reward processing. The system harnesses attention in the direction of cues for reward and simultaneously energizes goal-seeking behavior. It provides a mechanism through which neutral cues achieve “incentive salience” through primary and secondary association with rewarding events and thereby instigates action sequences that promote attainment of reward. Destruction of this system does not appear to eliminate the capacity to “enjoy” rewards, but it does eliminate interest in reward-related cues and in active pursuit of reward. Sensitization of this system through repeated and intense stimulation (e.g., ingestion of drugs) can lead to intense feelings of “wanting” (i.e., craving), resulting in compulsive drug-seeking behavior. Although the majority of research on reward prediction error and incentive salience models of the midbrain DA system has been conducted using food and psychoactive drugs as reward stimuli, there is evidence that this system plays a similar role with respect to other basic appetitive drives (e.g., thirst, sex; Horvitz, Richardson, & Ettenberg, 1993; Fiorino, Coury, & Phillips, 1997). Thus, on the basis of available evidence, there is reason to believe that the midbrain DA system comprises a core neural substrate of appetitive motivation, defined as mobilization for approach behavior (see Zisner & Beauchaine, this volume).

It bears repeating that distinct (albeit interconnected) neural structures appear to mediate the “liking” (hedonic) component of reward (i.e., the nucleus accumbens shell and ventral pallidum and the brainstem parabrachial nucleus to which these structures project). Berridge (2003) suggested that these structures, which are innervated by the mesolimbic DA system, may comprise a core “liking” circuit that participates in hedonic reactivity to a variety of reward stimuli. It should also be noted that other distinct brain structures contribute to mediation of overt consummatory behaviors tied to...
specific drive states. For example, fiber tracts running through the lateral and medial divisions of the hypothalamus play a crucial role in eating behavior (hunger and satiety, respectively), whereas the medial preoptic area of the hypothalamus appears to be especially crucial for sexual behavior.

**Interplay of Inhibitory Control and Reward/Incentive Circuitry in SUDs**

Drawing on the foregoing conceptions of control and appetite systems and relevant findings from neuroimaging, genetic, and developmental research, Karoly, Harlaar, and Hutchison (2013) advanced a compelling three-stage model of dysregulations in brain circuitry that give rise to and maintain substance-related addictions. The model considers interplay between inhibitory control circuitry and appetitive-motivational circuitry (termed “control network” and “incentive salience/reward network,” respectively) and their intersections with circuitry governing negative emotional states (e.g., irritability, distress, and dysphoria). In particular, the model describes how the relative influence exerted by control and incentive/reward networks shifts in the progression from recreational to urge-driven use, leading to withdrawal-related negative affect that contributes further to imbalance between the control and incentive reward networks.

The model distinguishes three distinct stages in the addiction cycle. In the binge/intoxication stage (1), use of substances is driven mainly by impulsive proclivities and (expected) positive effects of the drug. With continuing regular use, processes associated with the incentive/reward system (i.e., sensitization) increase in strength, with concomitant diminish in strength of control functions, thus leading to less-regulated use. The result is a transition toward the withdrawal/negative affect stage (2), at which point withdrawal following use produces increased activation in negative motivational systems (i.e., the amygdala and affiliated circuitry), which feeds back to control and incentive reward networks. The result is even greater predominance of urge-driven use, leading to a preoccupation/anticipation stage (3) during which substance use is driven mainly by compulsion as opposed to ad hoc pleasure-seeking. Here, strength of the incentive reward network has increased to a level that renders influence of the control network ineffective.

Importantly, Karoly et al.’s (2013) three-stage model emphasizes the dynamic interplay between alterations in neural function that occur with sustained engagement in drug-taking behavior and dispositional factors that affect susceptibility to processes at particular stages. Although its focus is on processes occurring after initiation of substance use, some consideration is given to factors that predispose to initial and continuing use. Individual differences in impulsive risk-taking and sensitivity to the unconditioned pleasurable effects of particular drugs are likely to be particularly important for entry into Stage 1. The authors draw attention in particular to research demonstrating reduced frontal brain activation during performance of tasks requiring inhibition of prepotent responses (e.g., antisaccade, go/no-go) among youth who are at risk for later development of SUDs as evidence for a role of weak inhibitory control capacity at this initial point. Yet the possibility exists that control network deficits evident at the time of adolescence could arise in some or perhaps even most cases from incentive/reward network impairments present earlier in life (see section below titled “P3 Brain Response and the Nature of Disinhibitory Liability”; cf. Beauchaine & McNulty, 2013).

**An Externalizing Spectrum Model Perspective on Disinhibitory Liability and Its Alternative Phenotypic Expressions**

We now return to the question of what general vulnerability to externalizing problems entails, both neurobiologically and psychologically, and we consider which factors shape such vulnerability into SUDs compared to other outcomes. Clearly, impulsivity and emotion dysregulation, which typify disorders in the externalizing spectrum, point to prefrontal brain dysfunction as a key mechanism underlying general disinhibitory liability (see also Beauchaine & McNulty, 2013; Beauchaine, McNulty, & Hinshaw, this volume). As noted earlier, lesions to frontal brain regions result in impulsive, externalizing behaviors, and poor performance on neuropsychological tests that assess frontal lobe function are evident across the externalizing spectrum. Both Morgan and Lilienfeld (2000) and Ogilvie, Stewart, Chan, and Shum (2011) reported meta-analytic evidence for robust deficits on frontal lobe tasks among individuals with conduct disorder and adult antisocial behavior. Individuals at risk for alcoholism by virtue of a positive parental history show similar impairments (Peterson & Pihl, 1990; Tarter, Alterman, & Edwards, 1985). Furthermore, reduced activity in frontal brain regions during inhibitory task performance characterizes symptomatic adolescents who later develop alcohol problems (Norman et al., 2011). Elsewhere, Barkley
(1997), based on an extensive review of neuropsychological studies, proposed that frontal brain dysfunction characterizes the hyperactive-impulsive and combined subtypes of attention-deficit/hyperactivity disorder (ADHD), with a primary role for deficits in response inhibition.

Perhaps more crucially, a twin study by Young et al. (2009) demonstrated a robust negative association between scores on a general externalizing factor subsuming impulse-related problems of differing types (assessed via informant report and interview)—combined with a scale measure of novelty seeking—and scores on a common executive-function (EF) factor defined by performance on three inhibitory control tasks known to index EF (i.e., antisaccade, Stroop, stop-signal; Miyake & Friedman, 2012). Data for the inhibitory control tasks were collected at age 17; scores for the externalizing variables were based on data from age 17 together with data collected at earlier ages. The twin design of the study allowed for decomposition of scores on both the externalizing factor and the EF factor into variance attributable to heritable versus shared and nonshared environmental influences. The correlation between heritable variance from the disinhibitory factor and heritable variance from scores on the EF factor was -.61. Thus, a heritable propensity toward externalizing problems was associated with heritable deficits in EF. This work provides compelling evidence that general externalizing vulnerability reflects a heritable impairment in the capacity to inhibit prepotent responses, possibly reflecting a basic, constitutional weakness in the frontal-control network described by Karoly et al. (2013).

Another brain region playing a role in disinhibitory psychopathology is the ACC, a structure that operates in concert with the PFC to guide behavior. As described earlier, the ACC functions to monitor ongoing action sequences and to anticipate and detect errors. Notably, the error-related negativity (ERN), a brain potential response that occurs following performance errors in a speeded reaction time task and is mediated in part by the ACC (Miltner, Braun, & Coles, 1997; Holroyd, Dien, & Coles, 1998; Luu, Flaisch, & Tucker, 2000), shows reduced amplitude among high-externalizing individuals (Hall, Bernat, & Patrick, 2007; see also Dikman & Allen, 2000; Pailing & Segalowitz, 2004). Furthermore, neuroimaging studies indicate the ACC is not activated during extinction of previously rewarded behaviors among externalizing males (Gatzke-Kopp et al., 2009), a finding that also points toward deficiencies in error monitoring. The hippocampus, another structure that operates in conjunction with the PFC to guide behavior (cf. Miller & Cohen, 2001), may also be dysfunctional among externalizing individuals (e.g., Raine et al., 2004; Soderstrom, Tullberg, Wikkelsoe, Ekholm, & Forsman, 2000).

An underlying weakness in the PFC and regions with which it interacts would be likely to confer a propensity to act on the basis of salient cues in the immediate environment rather than on the basis of internal representations of goals and methods for achieving them. In particular, dysfunction in the PFC and affiliated systems would compromise an individual's ability to (a) ascribe incentive salience to representations for more complex, distal, but ultimately more fulfilling behavioral goals; (b) anticipate obstacles and formulate strategies for overcoming them before they become overwhelming (e.g., deal proactively with frustrating or threatening circumstances); (c) detect conflict between competing response tendencies (i.e., recognize, online, the probability of making an error); and (d) monitor and regulate affective responses in the service of remote goals. Such a weakness would contribute to a range of impulse-related problems because it would produce an active response style centered on immediate cues in the environment and short-term gratification. Individuals would lack the capacity to pursue complex goals and long-term strategies.

However, although evidence for frontal control network deficits among externalizing individuals is extensive and compelling, it has been suggested that control network deficits might actually be the developmental consequence of a more basic neural dysfunction. Specifically, citing evidence from a variety of sources, Beauchaine and McNulty (2013) postulated that a weakness in the mesolimbic (midbrain) DA system, entailing reduced availability of DA in the ventral tegmental area (VTA) and pathways connecting it to the nucleus accumbens, along with impaired functional connectivity between this system and the mesocortical (VTA→frontal cortex) system, comprises a core neural substrate for disinhibitory liability (which they term “trait impulsivity”). Part of the basis for this argument is that the mesolimbic DA system is an earlier maturing network that provides foundational neural input via direct and indirect afferent pathways to the later maturing frontal control network. A constitutional weakness in this system, the authors argue, would establish a primal orientation toward immediate
over remote reward that, in turn, would compromise normal development of the mesocortical system essential to inhibitory control. As noted earlier, others (e.g., Miller & Cohen, 2001) have proposed that input to the PFC from the DA system provides the motivational impetus for biasing influences exerted by the PFC (i.e., in the service of goal attainment).

As partial evidence for their hypothesis, Beauchaine and McNulty (2013) reference extensive and well-replicated findings from studies demonstrating reduced mesolimbic DA transporter and D2/D3 receptor binding and blunted reactivity of mesolimbic and mesocortical systems to incentives among individuals with externalizing problems including ADHD (cf. Bush, Valera, & Seidman, 2005; Dickstein, Brannon, Castellanos, & Milham, 2006), conduct disorder (e.g., Rubia et al., 2009), and SUDs (e.g., Martin-Soolch et al., 2001; Volkow et al., 2004, 2012). Seemingly at odds with such findings, Buckholz et al. (2010a) reported that individuals high on the impulsive-antisociality dimension of the Psychopathic Personality Inventory, a dispositional factor closely related to the concept of externalizing proneness or disinhibitory liability (Blonigen, Hicks, Krueger, Patrick, & Iacono, 2005; see also Patrick, Fowles, & Krueger, 2009; Patrick, Hicks, Krueger, & Lang, 2005), showed enhanced release of DA within the nucleus accumbens in response to amphetamine administration together with augmented reactivity of the nucleus accumbens during anticipation of reward in a monetary incentive delay task. However, the Buckholz et al. results can be reconciled with Beauchaine and McNulty if (a) one conceives of the monetary incentive delay task as an “immediate” as opposed to “remote” reward task (i.e., involving presentation of cue for impending, certain reward outcomes) and enhanced DA release to amphetamine as compensatory to weak DA availability under normal resting conditions, or (b) impulsive antisocial individuals are exhibiting sensitization to amphetamines as described by Robinson and Berridge (see earlier discussion). Supporting possibility (a), another study by the same research group (Buckholz et al., 2010b) reported enhanced release of DA in the striatum following amphetamine administration in conjunction with diminished midbrain D2/D3 receptor binding potential at baseline in participants higher as compared to lower in trait impulsivity as measured by the Barrett Impulsiveness Scale (Barratt, Stanford, Dowdy, Liebman, & Kent, 1999). This pattern of results fits with the interpretation of enhanced DA response to amphetamine as compensatory to low baseline DA availability in impulsive-externalizing individuals (see next section on normalizing effects of DA-enhancing stimulant drugs on impulsive behavior, and affiliated brain response deficits, in individuals with ADHD).

**Reduced P300 Amplitude and Disinhibitory Liability**

Prefrontal control system/EF and incentive system/DA perspectives as core bases of disinhibitory psychopathology are interesting to consider in relation to the best-established neural indicator of externalizing proneness among adults—namely, reduced amplitude of the P3 brain potential response. (The term “P3” is used here for a set of brain potential components including the P3 response to attended target stimuli in variants of the well-known oddball task [termed “P300,” or “P3b”] and the P3 response to unexpected novel events [termed “novelty P3,” or “P3a”]). Although initially investigated as a possible indicator of biological risk for alcoholism (Begleiter, Porjesz, Bihari, & Kissin, 1984), further research revealed reduced P3 responses to be associated with various disinhibitory conditions including adult APD, child conduct disorder and ADHD, and dependence on other drugs (cf. Iacono, Malone, & McGue, 2003). In turn, studies demonstrating a coherent heritable factor underlying such conditions suggest that P3 might represent a neural indicator of this general liability factor.

As compelling support for this hypothesis, Patrick et al. (2006) reported that externalizing proneness, as indexed by scores on the factor in common among differing disinhibitory disorders, was associated negatively with amplitude of P3 responding to target stimuli in a visual oddball task, and this association accounted for relations of all individual disorders with P3. In a subsequent large-sample (N = 1,196) twin analysis, Hicks et al. (2007) demonstrated that the relation between general externalizing proneness and oddball P3 response was mediated almost entirely by heritable influences (see also Yancey, Venables, Hicks, & Patrick, 2013). Other follow-up work demonstrates reduced P3 responses among externalizing-prone college students and community adults to stimuli of other types across differing tasks—including novel nontargets within a three-stimulus oddball task, feedback stimuli within a choice-gambling task, stimulus arrays within a flanker discrimination task, and incidentally occurring noise probes within a picture-viewing task (Bernat, Nelson, Steele, Gehring, & Patrick, 2011; Nelson, Patrick, & Bernat, 2011; Patrick et al., 2013b).
Findings along these lines, in conjunction with work demonstrating that reduced P3 in presymptomatic at-risk youth predicts later development of diagnosable externalizing problems (e.g., Berman, Whipple, Fitch, & Noble, 1993; Hill, Steinhauer, Lowers, & Locke, 1995; Iacono, Carlson, Malone, & McGue, 2002), point to reduced P3 amplitude as a robust neural indicator of disinhibitory liability. However, the underlying neuropsychological processes are unclear. One challenge to interpretation is that the P3 is a broadly distributed cortical potential that reflects coordinated activity in multiple brain systems—with variants of P3 (e.g., novelty P3a, target P3b) differing in topography and presumed neural sources (Polich, 2007). Another challenge is that reductions in amplitude associated with externalizing proneness represent only a fraction of the overall systematic (e.g., temporally reliable, heritable) variance in P3 response (Yancey et al., 2013), rendering it unclear whether processing parameters known to affect P3 generally (i.e., across subjects) are the basis of externalizing-related variation. Certainly, one perspective on reduced P3 in relation to externalizing conditions is that it reflects, either directly or indirectly, impairments in functioning of inhibitory control systems in the brain (e.g., Begleiter & Porjesz, 1999; Iacono, Carlson, & Malone, 2000; see also Giancola & Tarter, 1999; Polich, 2007). Consistent with this perspective, there is evidence for executive dysfunction (including impaired inhibitory task performance) linked to reduced P3 amplitude in young individuals exhibiting externalizing problems (e.g., Kim, Kim, & Kwon, 2001; Roca et al., 2012).

At the same time, other evidence points to a role of the midbrain DA system in P3 responding. Evidence for a direct role of input from the midbrain DA system is especially strong for the more fronto-centrally distributed novelty P3 (P3a) variant (cf. Polich, 2007). A prominent role for noradrenergic activity, associated with the locus coeruleus in particular, has been posited for the more parieto-centrally distributed target-elicited (or, more broadly, task-relevant) P3b (Nieuwenhuis, Aston-Jones, & Cohen, 2005), but evidence exists as well for some role of the midbrain DA system in P3b. For example, diminished amplitude of both P3a and P3b response is observed among patients with Parkinson’s disease (Antal, Dibó, Kéri, Gábor, & Janka, 2000; Poceta, Houser, & Polich, 2006; Wang, Kuroiwa, & Kamitani, 1999), a degenerative condition resulting from depletion of DA-producing cells in the substantia nigra region of the midbrain. It is also present among individuals with restless leg syndrome (Jung et al., 2011; Poceta et al., 2006), a condition also associated with reduced DA function (Trenkwalder & Winkelmann, 2003). Regarding externalizing conditions, administration of methylphenidate—a DA agonist that increases synaptic DA availability (Cooper, Bloom, & Roth, 2003) and reduces symptoms of ADHD (Faraone, Spencer, Aleardi, Pagano, & Biederman, 2004; Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008)—produces normalizing effects on abnormalities in P3 response associated with ADHD (e.g., Hermens et al., 2005; Verbaten et al., 1994). Of further note, ADHD is associated both with restless leg syndrome (Cortese et al., 2005) and with patterns of sleep disturbance that are in turn associated with abnormal P3 responding under normal waking conditions (Salmi et al., 2005; Sangal & Sangal, 1997). Sleep patterns themselves are known to be subject to DA system influence (e.g., Dzirasa et al., 2006).

Although the foregoing lines of evidence point to a possible role for DA dysfunction in P3 response deficits associated with externalizing proneness, notable inconsistencies are evident across studies, and these need to be reconciled before stronger conclusions can be drawn. These include differences in task paradigms used to assess P3 response, inconsistencies in findings for P3a versus P3b in some studies, and inconsistencies in findings for P3 amplitude versus latency in other studies. There are other reasons, as well, to suppose that the association between externalizing proneness and P3 response may not be attributable exclusively to DA dysfunction. For one thing, as noted earlier, the locus coeruleus-norepinephrine system has been implicated more strongly in P3b response than any DA system. Relatedly, regarding the normalizing effects of methylphenidate on P3 response in ADHD, this medication exerts dose-dependent effects on noradrenergic neurotransmission as well (Kuczenski & Segal, 1997). More broadly, as discussed later, other perspectives on the basis of the broad liability toward disinhibitory problems and its relationship to deficient P3 response may be useful to consider in complement to the DA dysfunction hypothesis.

Alternative Addictive and Aggressive Expressions of General Disinhibitory Liability

The model of externalizing behavior set forth by Krueger et al. (2007) provides a useful point of reference for thinking about general disinhibitory
liability (trait disinhibition) and its role in SUDs. The model demonstrates that when externalizing problems are considered in terms of thematically distinct traits and problem tendencies, rather than as “disorders” encompassing multiple, loosely related symptoms, a multifactor structure emerges in which tendencies toward callous aggressiveness and problematic use of substances are each associated with a general externalizing factor and as well with a subsidiary factor separable from this general factor. As suggested by Krueger et al. (2007), and expanded upon in subsequent writings (e.g., Patrick, Durbin, & Moser, 2012; Patrick et al., 2009; Venables & Patrick, 2012), this structure suggests that tendencies to act against others in callous-uncaring ways and to use alcohol and drugs in excess arise in part from general disinhibitory liability—but additionally, in each case, reflect the shaping impact of other coherent influences distinct from this broad liability.

In the case of the callous-aggression subfactor of the externalizing spectrum model, an obvious connection exists to the literature on psychopathic personality. As discussed by Patrick et al. (2009), most measures of psychopathy designed for adults include representation of callous-uncaring (e.g., coldhearted, antagonistic; Lilienfeld & Widows, 2005; Lynam & Dereffinko, 2006) tendencies, and the scales that demarcate the ESI callous-aggression subfactor (in particular, empathy-reversed, relational and destructive forms of aggression, and excitement seeking, rebelliousness, and dishonesty; Krueger et al., 2007; Patrick et al., 2013) mirror symptoms and behavioral correlates of the “callous-unemotional traits” construct described in the child psychopathy literature (Frick & Marsee, 2006; Frick, Ray, Thornton, & Khan, 2014). What distinct etiologic influence(s) might contribute to expression of general disinhibitory liability in this direction? Broadly speaking, influences that promote use of force or exploitation as a means to achieve gratification or relief from distress would operate to shape disinhibitory tendencies toward an active aggressive (i.e., callous/psychopathic) expression (cf. Verona & Patrick, 2015). Influences of this sort could include distinct dispositional characteristics (e.g., low fear temperament [Frick & Marsee, 2006]; weak affiliative capacity [Patrick et al., 2009]), physical strength or size, and environmental factors (e.g., early physical abuse; modeling by others). This expression of disinhibitory liability could be termed a predation/antagonism pathway.

From the perspective of the externalizing spectrum model, influences that contribute to expression of disinhibitory liability toward SUDs are presumed to differ from those contributing to callous-aggressive outcomes. This supposition follows from the observation that callous-aggressive and substance-abuse tendencies are unrelated within the model, apart from their joint association with general externalizing tendencies. Clearly, factors that promote initial and continuing use of alcohol and/or drugs as a means to achieve gratification or relief from immediate distress would operate to shape disinhibitory tendencies in the SUD direction (Karoly et al., 2013). The relative loadings of content-relevant scales on the substance abuse subfactor of the ESI model provide some clues as to the nature of such influences. Per table 5 of Krueger et al. (2007), scales indexing marijuana use and other drug use load most strongly on this substance abuse subfactor, followed by the marijuana problems scale (reflecting dependency and adverse consequences from use). The implication is that this subfactor reflects a proclivity to seek out illicit drugs of differing types (more so than alcohol) and to engage in regular use of those that are most readily available (marijuana, in particular) to the point of dependency and problems. Notably, findings from a 25-year longitudinal study by Fergusson, Boden, and Horwood (2008) indicate that use of cannabis during late adolescence through early adulthood predicts later use of other illicit drugs above and beyond other variables (including psychosocial variables, personality traits, and conduct/attentional problems as assessed by parent/teacher report). Factors that may contribute to this proclivity include access to channels for obtaining illegal substances (e.g., relatives, deviant peers; Gillespie, Neale, & Kendler, 2009) and physical/psychological enjoyment of the consciousness and mood-altering effects of such drugs. Accordingly, this directional expression of disinhibitory liability could be described as a pleasure/hedonism pathway.

A key question in this regard is whether any heritable trait tendencies aside from general disinhibitory liability contribute to the proclivity to try and continue using drugs of differing types, in particular illegal ones (i.e., marijuana and other drugs; cf. Krueger et al., 2007). For example, it is clear that stable variations exist in the tendency of the midbrain DA “wanting” pathway to become sensitized to discrete cues for reward that affect susceptibility to drugs. In work with rodents, Flagel, Watson, Akil, and Robinson
(2008) demonstrated that animals drawn more to cues predictive of food reward than to the location of reward delivery showed increased psychomotor sensitization to repeated administrations of cocaine. Other work by this group (Flagel et al., 2011) has shown that this bias toward tracking reward cues is associated with increased release of DA to such cues. However, it remains to be determined whether increased susceptibility to DA incentive sensitization and general disinhibitory liability are the same or different. Another possible contributor to the “appetite” for drugs, apart from trait disinhibition, may be variation in unconditioned pleasurable responses to psychoactive drugs of differing types, as determined by the basal forebrain/hindbrain “liking” system (Berridge, 2003). For example, deficits in the liking system associated with major depression and manifested in symptoms of anhedonia and impaired reward learning may serve as a distinct source of motivation for drug use (i.e., to attain pleasurable experiences not achievable in other ways; Baskin-Sommers & Foti, 2015).

Behavior genetics studies conducted to date are equivocal on the question of whether a dispositional liability for SUDs (in particular, illicit drug use/problems) exists that is distinct from trait disinhibition. As noted earlier, Kendler et al. (2003a) found evidence for a single heritable factor contributing to covariance among abuse/dependence diagnoses for illegal substances of six types (cannabis, cocaine, hallucinogens, sedatives, stimulants, opiates). However, contrasting results were obtained in another twin study in which alcohol dependence and other drug abuse/dependence were examined in modeling analyses that also included conduct disorder, adult antisocial behavior, major depression, and anxiety disorders of differing types (Kendler et al., 2003b). Evidence was found for both a common heritable factor and more specific heritable factors that contribute separately to alcohol versus drug problems. Additional common factors contributing distinctively to anxiety-misery (depression, generalized anxiety) and fear (phobias, panic) were also found. In other work, Kendler, Myers, and Prescott (2007) modeled symptom data for assorted illicit (cannabis, cocaine) and licit substances (alcohol, caffeine, nicotine) and found evidence for separate, albeit correlated heritable factors contributing to abuse/dependence of drugs within each class. Cannabis and cocaine were associated, at similarly high degrees (.8 each), with the illicit-drug heritable factor, whereas alcohol was linked most strongly (.7) to the licit-drug heritable factor, followed by nicotine (.5), then caffeine (.15). Alcohol and nicotine also showed stronger bivariate associations with illicit drugs than with caffeine, indicating that interrelations among this group of drugs accounted mainly for the high correlation (.8) between the two heritable factors. Evidence was also found for distinct additive heritable influences contributing to problems with drugs of each type—appreciably in the case of nicotine and caffeine and more modestly in the case of cannabis, cocaine, and alcohol.

Findings from this latter study by Kendler et al. (2003b, 2007) point to a coherent heritable component to cannabis and other illegal drug abuse/dependence, separate from that associated with alcohol and nicotine. However, without additional nonsubstance indicators of externalizing proneness in the model (e.g., child conduct problems, adult antisocial behavior, disinhibitory traits), it remains unclear how the two heritable factors relate to general disinhibitory liability and whether the proclivity to use illegal drugs reflects heritable tendencies separate from this general liability. In an effort to address this question, we undertook biometric analyses of ESI scale data from a sample of adult twins (N = 476) who comprised a subset of participants from a study by Kramer et al. (2012). Scores on the 23 ESI scales for this twin sample were combined with scores for the full participant sample (N = 1,787) from Krueger et al. (2007), and the resulting dataset was used to specify the bifactor model, as described in Patrick et al. (2013a). Manifest scores on the three ESI factors (general disinhibition factor and subfactors corresponding to callous-aggression and substance abuse, parameterized as independent of one another) were computed for participants in the twin sample using maximum likelihood estimation. Contributions of heritable and environmental influences to scores for each factor were then evaluated through univariate biometric ACE models fit to the cross-twin, within-trait covariances.

As anticipated, estimated scores for the general disinhibitory factor were appreciably heritable, with the coefficient for influences of this type in the biometric model exceeding .5. Moreover, a significant contribution of heritable influence was found for scores on the substance abuse subfactor—with a coefficient exceeding .3. These results provide preliminary evidence for a contribution of coherent heritable influences—apart from
general disinhibitory liability—to the proclivity to abuse substances of differing types, particularly cannabis and other illicit drugs.

Unresolved Questions and Directions for Research General Disinhibitory and SUD-Specific Liabilities

The central unresolved question that emerges out of the current review is whether a coherent heritable liability toward drug and alcohol problems exists apart from the general liability that contributes to disinhibitory problems as a whole. Available data indicate that there are likely to be specific heritable influences that affect proneness to use of particular substances (e.g., cocaine vs. marijuana vs. alcohol; Kendler et al., 2012); such influences may either be promotive (e.g., Saccone et al., 2007) or protective (e.g., Shen et al., 1997). Still, is there a genotypic proclivity that shapes general disinhibitory liability toward substance abuse outcomes broadly? Or, stated more prosaically, is there a distinct heritable “appetite” for the psychoactive effects of pharmacologic agents that facilitates rapid and powerful “bonding” with such agents?

Cumulative research evidence to date indicates that questions regarding the etiology of SUDs and other externalizing conditions are likely to be addressed most effectively by considering conditions of these types in relation to one another, rather than in isolation. For example, the picture that emerges of the etiology of SUDS differs depending on whether modeling analyses focus on illegal drugs only (Kendler et al., 2003a), licit as well as illicit drugs of differing types (Kendler et al., 2007), or SUDS in conjunction with other forms of psychopathology (Kendler et al., 2003b). Regarding disinhibitory conditions as a whole, the externalizing spectrum model highlights the possibility that callous-psychopathic behavior and substance abuse are each determined in part by reckless-impulsive proclivities associated with general disinhibitory liability—but that other dispositional tendencies intersect with this general liability to shape its expression in one direction or the other. As with work focused on the etiologic basis of illegal drug abuse per se (e.g., Kendler et al., 2003a), behavior genetic research focusing on antisocial behavior indicates that the configuration of impulsive conduct problems together with callous-unemotional tendencies constitutes a highly heritable phenotype (Viding, Blair, Moffitt, & Plomin, 2005). However, it must be presumed that heritable influences contributing to this phenotype overlap substantially with those that contribute to abuse of illegal drugs of differing types. Given this, it will be necessary to examine externalizing conditions of various types together in a joint etiological model in order to clearly establish which heritable influences contribute in common to SUD and callous-aggressive outcomes, and whether and to what degree other heritable factors (vs. distinct environmental influences) shape the expression of shared disinhibitory proclivities in one direction or the other.

Findings from our preliminary twin-sample analysis of scores on the general disinhibition factor and substance abuse subfactor from the externalizing spectrum model suggest separate sources of genetic influence contributing to each. However, interpretations are constrained by several key limitations, including reliance on a modest sample size, purely questionnaire-based assessment of externalizing tendencies, and the cross-sectional nature of the data (i.e., all scale measures were collected at a single point, in adulthood). A more compelling answer to this overall question will require a systematic multidomain, longitudinal developmental approach.

A crucial foundation for systematic developmental research on the etiology of SUDs exists in work undertaken by Vanyukov et al. (2003, 2009) to operationalize general disinhibitory liability early in life through a transmissible liability index (TLI). Consisting of a composite of self- and other-report (i.e., parent, teacher) indicators of non–substance-themed behavioral tendencies that differentiate between offspring of parents with and without SUDs, scores on the TLI measure are substantially heritable (Vanyukov et al., 2009) and prospectively predict emergence of substance-related problems from earlier to later life (Kirisci et al., 2009; Vanyukov et al., 2009). This work demonstrates that proneness toward development of substance problems can be quantified well before the emergence of such problems—as early as age 10 (Kirisci et al., 2009) and perhaps even earlier if based entirely on data from informant raters. Notably, recent longitudinal-twin research by Hicks, Iacono, and McGue (2012) shows that a close variant of the TLI exhibits a level of heritability more comparable to an aggregate measure of non-SUD externalizing tendencies (i.e., estimated A > .7) than to a composite of SUD symptoms (estimated A < .5) and prospectively predicts non-SUD externalizing behaviors even more strongly than SUD outcomes. The implication is that the TLI may tap general disinhibitory liability rather than SUD liability per se. Either way,
availability of a measure of this type for quantifying liability at early ages creates avenues for many interesting and potentially profitable lines of research.

One valuable focus will be to examine relations across time of early liability as indexed by TLI scores with biological and behavioral variables including (a) DA availability in the mesolimbic system at baseline and reactivity of mesolimbic structures (e.g., VTA, nucleus accumbens) to DA agonists and cues for reward; (b) differing variants of P3 response; (c) task-behavioral measures of EF, including performance on inhibitory control paradigms (cf. Young et al., 2009); and (d) attention-allocation and brain reactivity to reward signals versus goal locations in a human analog version of the “sign-tracking” task used by Flagel and colleagues (2008, 2011). Also of central importance will be work on interrelations from earlier to later ages between indices of mesolimbic DA system function (e.g., baseline receptor binding and phasic cue reactivity) and measures of executive-inhibitory function, along with the mediating role these functional domains play across time in general disinhibitory tendencies (assessed via non-SUD/nonaggressive indicators), substance abuse, and callous-aggressive behavior. In conjunction with ongoing behavioral and molecular genetics studies, such work can help to establish whether the root source of disinhibitory liability lies in limbic system dysfunction or frontal-control system deficits (or perhaps both)—and whether separate dispositional factors operate over time to shape this general liability toward SUD outcomes.

P3 Brain Response and the Nature of Disinhibitory Liability

Another crucial question is what the general liability to impulse-control problems—variously referred to as externalizing (Krueger et al., 2002), externalizing proneness (Nelson et al., 2011), disinhibition (Iacono, Carlson, Taylor, Elkins, & McGue 1999), trait impulsivity (Beauchaine & McNulty, 2013), or deficient self-control (Gottfredson & Hirschi, 1990)—entails in psychological and biobehavioral terms. The nature of this general liability has been characterized in differing ways depending on the clinical phenomena of main interest and the range and types of evidence considered. For example, Vanyukov et al. (2012) characterized the “common liability to addiction” as entailing “an identifiable circumscribed group of mechanisms underlying behavioral regulation and socialization” (p. S6). These authors highlight a strong role for self-selection of experience (i.e., gene–environment correlation) in the phenotypic expression of this core liability. From this perspective, the externalizing-prone individual is, in the words of Ponzi (1934), born “looking for trouble.” Drawing on evolutionary theory, Vanyukov et al. postulate that the basis of disinhibitory liability is a nervous system overadapted for survival in a highly volatile natural environment. Individuals with this biological orientation seek out change on an ongoing basis to compensate for a diminished affective response capacity: “[T]heir status of the nervous system is underarousal, resulting, e.g., in high novelty and sensation seeking (including that from substance use), risky and antisocial behavior, etc. This becomes emphasized particularly at transition to the reproductive period (which defines fitness) and relative independence, i.e., at adolescence.” (p. S11)

Other investigators have theorized about the nature of this general liability in the context of work on ADHD. As noted earlier, Beauchaine and McNulty (2013) posited in this context that disinhibitory liability (termed “trait impulsivity”) is rooted early in life in dysfunction of the mesolimbic DA system, which results in a bias toward immediate reward seeking. This tendency in turn compromises normal development of frontal control functions, which contributes to continued impulsivity across the life span. A related perspective was advanced by Nigg and Casey (2005). Focusing in particular on the variant of ADHD that involves impulsive-hyperactive tendencies combined with inattentiveness, these investigators proposed that the core liability entails deficits in “the ability to predict temporal and contextual structure in the environment” (p. 788) mediated by frontostriatal and frontocerebellar circuits of the brain. Particular emphasis is placed in this model on the delicate interplay between affective-subcortical and cognitive-prefrontal systems across sequential stages of development: Dysfunction from infancy in core circuitry required to recognize unexpected events and contingency shifts in the environment is thus detrimental to later-occurring development of prefrontal networks required for inhibitory control and planning. This conception is broader than Beauchaine and McNulty’s in that it posits a dysfunction in basic event detection/prediction systems, arising from alternative possible sources (“altered catecholaminergic modulation of the circuitry, altered prefrontal projections, or poor prediction-related functions presumably related to altered development of striatal and/or cerebellar neuronal regions or connections” [p. 791]), that has implications for punishment as well as reward learning.
From the perspective of Nigg and Casey (2005) and the general developmental principle of multifinality (Cicchetti & Rogosh, 1996), it may be most useful to conceive of general externalizing proneness (Krueger et al., 2002; Nelson et al., 2011; Young et al., 2009) as an emergent condition of executive-control dysfunction arising from alternative root sources that operate across time to compromise the formation of frontal regulatory networks. It is conceivable that the variance in P3 amplitude that intersects with externalizing proneness (Nelson et al., 2011), known to be attributable to common heritable influence (Hicks et al., 2007; Yancey et al., 2013), reflects this emergent condition of executive-control dysfunction. Patrick and Bernat (2009) hypothesized that reduced P3 amplitude reflects a failure to link and integrate ongoing stimulus events with cognitive/affective representations stored in long-term memory (cf. Ericsson & Kinsch, 1995), a normally automatic process that is crucial to anticipation, reflection, and self-regulation of emotion and behavior. Evidence for this comes from notable instances in which externalizing individuals show normal enhancement of early-latency brain response to affective versus neutral visual stimuli, indicating intact processing of motivational salience, followed by diminished amplitude of subsequent P3 response for stimuli of all types, indicating reduced postperceptual elaborative processing (Bernat et al., 2011; Olson, 2014; Patrick & Bernat, 2009). The implication is that part of P3 responsivity entails a “reaching out” between pre-existing representations of experience and perceptual-motivational processes instigated by ongoing stimulus events—and it is this natural interplay between stored representations and immediate processing that is reduced among externalizing individuals.

Systematic longitudinal research that employs measures from multiple domains (including self- and informant-report, behavioral performance, and neurophysiology) will be needed to clarify the nature and origins of executive-control dysfunction among externalizing-prone individuals and the psychological significance of reduced P3 amplitude vis-à-vis this dysfunction. Key questions include: (1) Can early functional deficits in core circuitry as described by Nigg and Casey (2005) be indexed in a manner that predicts later emergence of executive system impairments? (2) For individuals who exhibit early circuitry dysfunction associated with later executive impairment, does reduced P3 amplitude precede or emerge concurrently with executive impairment? (3) Would interventions that prevent the cascade from early circuitry dysfunction to executive system impairment leave P3 intact?

“Functional Addicts” and “Successful Psychopaths”

A further key issue that comes out of the externalizing spectrum framework, as illustrated in Figure 3.1, is whether differing degrees of disinhibitory liability in conjunction with varying levels of SUD or callous-aggressive shaping influences give rise to distinct symptom patterns. Earlier, we distinguished between pleasure/hedonism and predation/antagonism pathways toward which disinhibitory liability might progress, depending on shaping influences of one kind or another. Operating from this viewpoint, it is conceivable that high levels of SUD-specific (hedonism-promoting) or aggression-specific (antagonism-promoting) influences, in the absence of high disinhibitory liability, could give rise to substance-addicted or callous-psychopathic individuals capable of functioning effectively in many areas of life. For example, there are clearly examples of people who manage to achieve success in work and relationships despite finding drugs of one sort or another inescapably “precious” (in the words of Gollum, 2002). Likewise, there exist people who operate in ruthless, exploitative ways without concern for others, who achieve wealth or fame as opposed to ostracization or imprisonment. It can be hypothesized that individuals of these types, despite having excessive appetites for pleasure or power, have well-established extended working memory structures (cf. Ericsson & Kinsch, 1995) for goals and consequences that dysfunctional high-disinhibited persons lack. Systematic investigation of higher functioning cases of these types, along with individuals high in biological risk for externalizing psychopathology who manage to lead functional lives, can help to provide unique insight into factors that shape the expression of disinhibitory liability in alternative maladaptive directions or exert healthy compensatory effects.

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