CHAPTER

3 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, 2003*a*). 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 on illicit drugs (Kendler, Prescott, Myers, & Neale, 2003*b*). 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 normal development of inhibitory capacity (cf. Beauchaine & McNulty, 2013; Nigg & Casey, 2005), which contribute to other externalizing problems, including childhood disruptive behavior disorders (conduct 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., 2003*b*; 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., 2003*b*; 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: disconstraint, 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 disconstraint/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*b*; 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., 2013*a*) 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., 2013*a*). 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. (2013*a*) 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

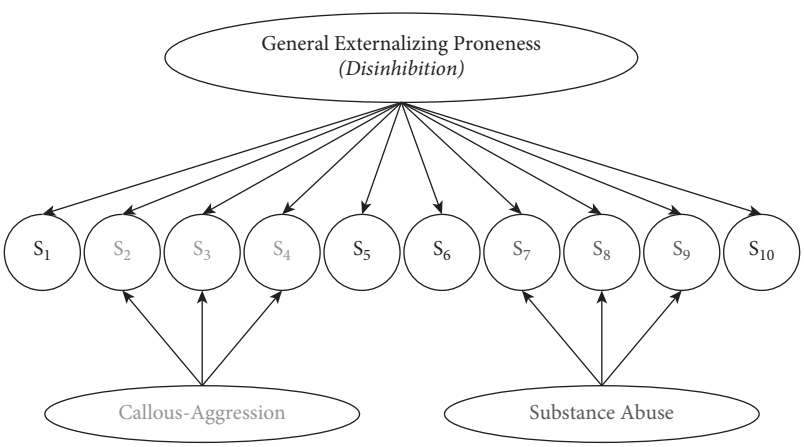

Figure 3.1 Schematic depiction of best-fitting confirmatory bifactor model of the Externalizing Spectrum Inventory (ESI; Krueger et al., 2007; Patrick et al., 2013a). The model is represented schematically because the 23 subscales of the ESI included in the model are too numerous to depict in full. Subscripted "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 proneness, were included in comparison with previous models focused on fewer (mostly disorder-related) indicators (Kendler et al., 2003*b*; 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 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, & Weiskrantz, 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 (Broerse, 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., by 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; Wagar & 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

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 (pleasurableness) 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 attenuation 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). From this, Berridge and Robinson conclude that midbrain DA neurons are not essential for reward learning, defined as changes in the hedonic value of rewards arising through associative pairings with other pleasurable or aversive stimuli. 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 appetitive 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 diminishment in the 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 presymptomatic 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 D_2/D_3 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-Soelch et al., 2001; Volkow et al., 2004, 2012). Seemingly at odds with such findings, Buckholtz et al. (2010*a*) 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 Buckholtz 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 this same research group (Buckholtz et al., 2010*b*) reported enhanced release of DA in the striatum following amphetamine administration in conjunction with *diminished* midbrain D_2/D_3 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., 2013*b*).

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 parietally 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 & Derefinko, 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*b*) 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. (2003*a*) 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., 2003*b*). 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. (2003*b*, 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. (2013*a*). 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., 2003*a*), 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., 2003*b*). Regarding disinihibitory 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., 2003*a*), 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 catecholinergic 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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References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Anderson, S. W., Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1999). Impairment of social and moral behavior related to early damage in the human prefrontal cortex. *Nature Neuroscience*, *2*, 1032–1037.

Antal, A., Dibó, G., Kéri, S., Gábor, K., & Janka, Z. (2000). P300 component of visual event-related potentials distinguishes patients with idiopathic Parkinson's disease from patients with essential tremor. *Journal of Neural Transmission*, *107*, 787–797.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unified theory of ADHD. *Psychological Bulletin*, *121*, 65–94.

Barratt, E. S., Stanford, M. S., Dowdy, L., Liebman, M. J., & Kent, T. A. (1999). Impulsive and premeditated aggression: A factor analysis of self-reported acts. *Psychiatry Research*, *86*, 163–173.

Baskin-Sommers, A. R., & Foti, D. (2015). Abnormal reward functioning across substance use disorders and major depressive disorder: Considering reward as a transdiagnostic mechanism. *International Journal of Psychophysiology*. doi: 10.1016/j.ijpsycho.2015.01.011

Beauchaine, T. P., & McNulty, T. (2013). Comorbidities and continuities as ontogenic processes: Toward a developmental spectrum model of externalizing psychopathology. *Development and Psychopathology*, *25*, 1505–1528.

Beauchaine, T. P., McNulty, T., & Hinshaw, S. P. (this volume). A biosocial developmental model of externalizing psychopathology across the lifespan. In T. P Beauchaine & S. P. Hinshaw (Eds.), *The Oxford handbook of externalizing spectrum disorders*. New York: Oxford University Press.

Beauregard, M., Levesque, J., & Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *Journal of Neuroscience*, *21*, RC165 (6993–7000).

Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *Journal of Neuroscience*, *18*, 428–437.

Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science*, *275*, 1293–1295.

Begleiter, H., & Porjesz, B. (1999). What is inherited in the predisposition toward alcoholism? A proposed model. *Alcoholism: Clinical and Experimental Research*, *23*, 1125–1135.

Begleiter, H., Porjesz, B., Bihari, B., & Kissin, B. (1984). Event-related brain potentials in boys at risk for alcoholism. *Science*, *225*, 1493–1496.

Berman, S. M., Whipple, S. C., Fitch, R. J., & Noble, E. P. (1993). P3 in young boys as a predictor of adolescent substance use. *Alcohol*, *10*, 69–76.

Bernat, E. M., Nelson, L. D., Steele, V. R., Gehring, W. J., & Patrick, C. J. (2011). Externalizing psychopathology and gain/loss feedback in a simulated gambling task: Dissociable components of brain response revealed by time-frequency analysis. *Journal of Abnormal Psychology*, *120*, 352–364.

Berridge, K. C. (2003). Pleasures of the brain. *Brain and Cognition*, *52*, 106–128.

Berridge, K. C., & Robinson, T. E. (1995). The mind of an addicted brain: Neural sensitization of wanting versus liking. *Current Directions in Psychological Science*, *4*, 71–76.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, *28*, 309–369.

Berridge, K. C., Venier, I. L., & Robinson, T. E. (1989). Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: Implications for arousal and anhedonia hypotheses of dopamine function. *Behavioral Neuroscience*, *103*, 36–45.

Blair, R. J., & Cipolotti, L. (2000). Impaired social response reversal. A case of "acquired sociopathy". *Brain*, *123*, 1122–1141.

Blonigen, D. M., Hicks, B. M., Krueger, R. F., Patrick, C. J., & Iacono, W. G. (2005). Psychopathic personality traits: Heritability and genetic overlap with internalizing and externalizing psychopathology. *Psychological Medicine*, *35*, 637–648.

Blonigen, D. M., Patrick, C. J., Douglas, K. S., Poythress, N. G., Skeem, J. L., Lilienfeld, S. O., . . . Krueger, R. F. (2010). Multimethod assessment of psychopathy in relation to factors of internalizing and externalizing from the Personality Assessment Inventory: The impact of method variance and suppressor effects. *Psychological Assessment*, *22*, 96–107.

Blumer, D., & Benson, D. F. (1975). Personality changes with frontal and temporal lobe lesions. In D. F. Benson & D. Blumer (Eds.), *Psychiatric aspects of neurological disease* (pp. 151–169). New York: Grune & Stratton.

Broerse, A., Crawford, T. J., & den Boer, J. A. (2001). Parsing cognition in schizophrenia using saccadic eye movements: A selective overview. *Neuropsychologia*, *39*, 742–756.

Brown, J. W., & Braver, T. S. (2005). Learned predictions of error likelihood in the anterior cingulate cortex. *Science*, *307*, 1118–1121.

Buckholtz, J. W., Treadway, M. T., Cowan, R. L., Woodward, N. D., Benning, S. D., Li, R., . . . Zald, D. H. (2010*a*). Mesolimbic dopamine reward system hypersensitivity in individuals with psychopathic traits. *Nature Neuroscience*, *13*, 419–421.

Buckholtz, J. W., Treadway, M. T., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S., . . . Zald, D. H. (2010*b*). Dopaminergic network differences in human impulsivity. *Science*, *329*, 532.

Burt, S. A., Krueger, R. F., McGue, M., & Iacono, W. G. (2001). Sources of covariation among attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder: The importance of shared environment. *Journal of Abnormal Psychology*, *110*, 516–525.

Bush, G., Valera, E. M., & Seidman, L. J. (2005). Functional neuroimaging of attention-deficit/hyperactivity disorder: A review and suggested future directions. *Biological Psychiatry*, *57*, 1273–1284.

Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D. N., & Cohen, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, *280*, 747–749.

Cicchetti, D., & Rogosh, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology*, *8*, 597–600.

Cohen, J. D., Forman, S. D., Braver, T. S., Casey, B. J., Servan-Schreiber, D., & Noll, D. C. (1994). Activation of prefrontal cortex in a nonspatial working memory task with functional MRI. *Human Brain Mapping*, *1*, 293–304.

Cohen, J. D., & O'Reilly, R. C. (1996). A preliminary theory of the interactions between prefrontal cortex and hippocampus that contribute to planning and prospective memory. In

M. Brandimonte, G. O., Einstein, & M. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 267–296). Mahwah, NJ: Erlbaum.

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., & Smith, E. E. (1997). Temporal dynamics of brain activation during a working memory task. *Nature*, *386*, 604–608.

Cohen, J. D., & Servan-Schreiber, D. (1992). Context, cortex, and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychological Review*, *99*, 45–77.

Cooper, J. R., Bloom, F. E., & Roth, R. H. (2003). *The biochemical basis of neuropharmacology* (8th ed). New York: Oxford University Press.

Corr, P. J., & McNaughton, N. (this volume). Neural mechanisms of low trait anxiety and risk for externalizing behavior. In T. P Beauchaine & S. P. Hinshaw (Eds.), *The Oxford handbook of externalizing spectrum disorders*. New York: Oxford University Press.

Cortese, S., Konofal, E., Lecendreux, M., Arnulf, I., Mouren, M. C., Darra, F., & Dalla Bernardina, B. (2005). Restless legs syndrome and attention-deficit/hyperactivity disorder: A review of the literature. *Sleep*, *28*, 1007–1013.

Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., & Damasio, A. R. (1994). The return of Phineas Gage: Clues about the brain from the skull of a famous patient. *Science*, *264*, 1102–1105.

Damasio, A. R., Tranel, D., & Damasio, H. (1990). Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behavioral Brain Research*, *41*, 81–94.

Davidson, R. J., Putnam, K. M., & Larson, C. L. (2000). Dysfunction in the neural circuitry of emotion regulation—A possible prelude to violence. *Science*, *289*, 591–594.

Davis, M., & Lee, Y. (1998). Fear and anxiety: Possible roles of the amygdala and bed nucleus of the stria terminalis. *Cognition and Emotion*, *12*, 277–305.

Dias, R., Robbins, T. W., & Roberts, A. C. (1996). Dissociation in prefrontal cortex of affective and attentional shifts. *Nature*, *380*, 69–72.

Dickstein, S. G., Brannon, K., Castellanos, X. F., & Milham, M. P. (2006). The neural correlates of attention-deficit/hyperactivity disorder: An ALE meta-analysis. *Journal of Child Psychology and Psychiatry*, *47*, 1051–1062.

Dikman, Z. V., & Allen, J. J. (2000). Error monitoring during reward and avoidance learning in high–and low-socialized individuals. *Psychophysiology*, *37*, 43–54.

Dzirasa, K., Ribeiro, S., Costa, R., Santos, L. M., Lin, S. C., Grosmark, A., . . . Nicolelis, M. A. L. (2006). Dopaminergic control of sleep-wake states. *Journal of Neuroscience*, *26*, 10577–10589.

Ericsson, K. A., & Kinsch, W. (1995). Long-term working memory. *Psychological Review*, *102*, 211–245.

Faraone, S. V., Spencer, T., Aleardi, M., Pagano, C., & Biederman, J. (2004). Meta-analysis of the efficacy of methylphenidate for treating adult attention-deficit/hyperactivity disorder. *Journal of Clinical Psychopharmacology*, *24*, 24–29.

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2008). The developmental antecedents of illicit drug use: Evidence from a 25-year longitudinal study. *Drug and Alcohol Dependence*, *96*, 165–177.

Fiorino, D. F., Coury, A. G., & Phillips, A. G. (1997). Dynamic changes in nucleus accumbens dopamine efflux during the Coolidge effect in male rats. *Journal of Neuroscience*, *17*, 4849–4855.

Flagel, S. B., Clark, J. J., Robinson, T. E., Mayo, L., Czuj, A., Willuhn, I., . . . Akil, H. (2011). A selective role for dopamine in stimulus-reward learning. *Nature*, *469*, 53–57.

Flagel, S. B., Watson, S. J., Akil, H., & Robinson, T. E. (2008). Individual differences in the attribution of incentive salience to a reward-related cue: Influence on cocaine sensitization. *Behavioral Brain Research*, *186*, 48–56.

Frick, P. J., & Marsee, M. A. (2006). Psychopathy and developmental pathways to antisocial behavior in youth. In C. J. Patrick (Ed.) *Handbook of psychopathy* (pp. 353–374). New York: Guilford.

Frick, P. J., Ray, J. V., Thornton, L. C., & Kahn, R. E. (2014). Can callous-unemotional traits enhance the understanding, diagnosis, and treatment of serious conduct problems in children and adolescents? A comprehensive review. *Psychological Bulletin*, *140*, 1–57.

Gatzke-Kopp, L., & Beauchaine, T. P. (2007). Central nervous system substrates of impulsivity: Implications for the development of attention-deficit/hyperactivity disorder and conduct disorder. In D. Coch, G. Dawson, & K. Fischer (Eds.), *Human behavior, learning, and the developing brain: Atypical development* (pp. 239–263). New York: Guilford.

Gatzke-Kopp, L. M., Beauchaine, T. P., Shannon, K. E., Chipman-Chacon, J., Fleming, A. P., Crowell, S. E., . . . Aylward, E. (2009). Neurological correlates of reward responding in adolescents with and without externalizing behavior disorders. *Journal of Abnormal Psychology*, *118*, 203–213.

Giancola, P. R., & Tarter, R. E. (1999). Executive cognitive functioning and risk for substance abuse. *Psychological Science*, *10*, 203–205.

Gillespie, N. A., Neale, M. C., & Kendler, K. S. (2009). Pathways to cannabis abuse: A multi-stage model from cannabis availability, cannabis initiation, and progression to abuse. *Addiction*, *104*, 430–438.

Goldman-Rakic, P. S. (1996). The prefrontal landscape: Implications of functional architecture for understanding human mentation and the central executive. *Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences*, *351*, 1445–1453.

Gollum (fictional character). (2002). In P. R. Jackson (Producer/Director), *The lord of the rings: The two towers*. New Zealand/USA: New Line Cinema.

Gottfredson, M. R., & Hirschi, T. (1990). *A general theory of crime*. Stanford, CA: Stanford University Press.

Hall, J. R., Bernat, E. M., & Patrick, C. J. (2007). Externalizing psychopathology and the error-related negativity. *Psychological Science*, *18*, 326–333.

Han, C., McGue, M. K., & Iacono, W. G. (1999). Lifetime tobacco, alcohol and other substance use in adolescent Minnesota twins: Univariate and multivariate behavioral genetic analyses. *Addiction*, *94*, 981–993.

Hermens, D. F., Williams, L. M., Clarke, S., Kohn, M., Cooper, N., & Gordon, E. (2005). Responses to methylphenidate in adolescent AD/HD: Evidence from concurrently recorded autonomic (EDA) and central (EEG and ERP) measures. *International Journal of Psychophysiology*, *58*, 21–33.

Hicks, B. M., Blonigen, D. M., Kramer, M. D., Krueger, R. F., Patrick, C. J., Iacono, W. G., & McGue, M. (2007). Gender differences and developmental change in externalizing

disorders from late adolescence to early adulthood: A longitudinal twin study. *Journal of Abnormal Psychology*, *116*, 433–447.

Hicks, B. M., Iacono, W. G., & McGue, M. (2012). Index of the transmissible common liability to addiction: Heritability and prospective associations with substance abuse and related outcomes. *Drug and Alcohol Dependence*, *123*, S18–S23.

Hicks, B. M., Krueger, R. F., Iacono, W. G., McGue, M., & Patrick, C. J. (2004). Family transmission and heritability of externalizing disorders: A twin-family study. *Archives of General Psychiatry*, *61*, 922–928.

Hill, S. Y., Steinhauer, S., Lowers, L., & Locke, J. (1995). Eight-year longitudinal follow-up of P300 and clinical outcome in children from high-risk for alcoholism families. *Biological Psychiatry*, *37*, 823–827.

Holroyd, C. B., Dien, J., & Coles, M. G. H. (1998). Error-related scalp potentials elicited by hand and foot movements: Evidence for an output-independent error-processing system in humans. *Neuroscience Letters*, *242*, 65–68.

Horvitz, J. C., Richardson, W. B., & Ettenberg, A. (1993). Dopamine receptor blockade and thirst produce differential effects on drinking behavior. *Pharmacology Biochemistry and Behavior*, *45*, 725–728.

Iacono, W. G., Carlson, S. R., & Malone, S. M. (2000). Identifying a multivariate endophenotype for substance use disorders using psychophysiological measures. *International Journal of Psychophysiology*, *38*, 81–96.

Iacono, W. G., Carlson, S. R., Malone, S. M., & McGue, M. (2002). P3 event-related potential amplitude and the risk for disinhibitory disorders in adolescent boys. *Archives of General Psychiatry*, *59*, 750–757.

Iacono, W. G., Carlson, S. R., Taylor, J., Elkins, I. J., & McGue, M. (1999). Behavioral disinhibition and the development of substance use disorders: Findings from the Minnesota Twin Family Study. *Development and Psychopathology*, *11*, 869–900.

Iacono, W. G., Malone, S. M., & McGue, M. (2003). Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. *International Journal of Psychophysiology*, *48*, 147–178.

Jung, K. Y., Koo, Y. S., Kim, B. J., Ko, D., Lee, G. T., Kim, K. H., & Im, C. H. (2011). Electrophysiologic disturbances during daytime in patients with restless legs syndrome: Further evidence of cognitive dysfunction? *Sleep Medicine*, *12*, 416–421.

Karoly, H. C., Harlaar, N., & Hutchison, K. E. (2013). Substance use disorders: A theory-driven approach to the integration of genetics and neuroimaging. *Annals of the New York Academy of Sciences*, *1282*, 71–91.

Kendler, K. S., Chen, X., Dick, D., Maes, H., Gillespie, N., Neale, M. C., & Riley, B. (2012). Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. *Nature Neuroscience*, *15*, 181–189.

Kendler, K. S., Jacobson, K. C., Prescott, C. A., & Neale, M. C. (2003*a*). Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *American Journal of Psychiatry*, *160*, 687–695.

Kendler, K. S., Myers, J., &, Prescott, C. A. (2007). Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. *Archives of General Psychiatry*, *64*, 1313–1320.

Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003*b*). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry*, *60*, 929–937.

Kim, M., Kim, J, & Kwon, J. S. (2001). Frontal P300 decrement and executive dysfunction in adolescents with conduct problems. *Child Psychiatry and Human Development*, *32*, 93–106.

Kirisci, L., Tarter, R., Mezzich, A., Ridenour, T., Reynolds, M., & Vanyukov, M. (2009). Prediction of cannabis use disorder between boyhood and young adulthood: Clarifying the phenotype and environtype. *American Journal on Addictions*, *18*, 36–47.

Kramer, M. D., Patrick, C. J., Krueger, R. F., & Gasperi, M. (2012). Delineating physiologic defensive reactivity in the domain of self-report: Phenotypic and etiologic structure of dispositional fear. *Psychological Medicine*, *42*, 1305–1320.

Krueger, R. F. (1999). Personality traits in late adolescence predict mental disorders in early adulthood: A prospective-epidemiological study. *Journal of Personality*, *67*, 39–65.

Krueger, R. F., Caspi, A., Moffitt, T. E., Silva, P. A., & McGee, R. (1996). Personality traits are differentially linked to mental disorders: A multi-trait, multi-diagnosis study of an adolescent birth cohort. *Journal of Abnormal Psychology*, *105*, 299–312.

Krueger, R. F., Hicks, B., Patrick, C. J., Carlson, S., Iacono, W. G., & McGue, M. (2002). Etiologic connections among substance dependence, antisocial behavior, and personality: Modeling the externalizing spectrum. *Journal of Abnormal Psychology*, *111*, 411–424.

Krueger R. F., Markon, K. E., Patrick, C. J., Benning, S. D., & Kramer, M. D. (2007). Linking antisocial behavior, substance use, and personality: An integrative quantitative model of the adult externalizing spectrum. *Journal of Abnormal Psychology*, *116*, 645–666.

Kuczenski, R., & Segal, D. S. (1997). Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: Comparison with amphetamine. *Journal of Neurochemistry*, *68*, 2032–2037.

LeDoux, J. E. (1995). Emotion: Clues from the brain. *Annual Review of Psychology*, *46*, 209–235.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, *23*, 155–184.

Lilienfeld, S. O., & Widows, M. R. (2005). *Psychopathic personality inventory–revised: Professional manual.* Lutz, FL: Psychological Assessment Resources.

Luu, P., Flaisch, T., & Tucker, D. M. (2000). Medial frontal cortex in action monitoring. *Journal of Neuroscience*, *20*, 464–469.

Lynam, D. R., & Derefinko, K. J. (2006). Psychopathy and personality. In C. J. Patrick (Ed.) *Handbook of psychopathy* (pp. 133–155). New York: Guilford.

MacDonald, A. W., III, Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, *288*, 1835–1838.

Malone, S. M., Taylor, J., Marmorstein, N. R., McGue, M., & Iacono, W. G. (2004). Genetic and environmental influences on antisocial behavior and alcohol dependence from adolescence to early adulthood. *Development and Psychopathology*, *16*, 943–966.

Martin-Soelch, C., Leenders, K. L., Chevalley, A. -F., Missimer, J., Kunig, S., Magyar, A., Mino, A., & Schultz, W. (2001). Reward mechanisms in the brain and their role in dependence: Evidence from neurophysiological and neuroimaging studies. *Brain Research Reviews*, *36*, 139–149.

McClure, S. M., Daw, N. D., & Montague, P. R. (2003). A computational substrate for incentive salience. *Trends in Neurosciences*, *26*, 423–428.

Miller, E. K. (1999). The prefrontal cortex: Complex neural properties for complex behavior. *Neuron*, *22*, 15–17.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202.

Miltner, W. H. R., Braun, C. H., & Coles, M. G. H. (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence for a "generic" neural system for error detection. *Journal of Cognitive Neuroscience*, *9*, 788–798.

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions four general conclusions. *Current Directions in Psychological Science*, *21*, 8–14.

Montague, P. R., Dayan, P., & Sejnowski, T. J. (1996). A framework for mesecephalic dopamine systems based on predictive Hebbian learning. *Journal of Neuroscience*, *16*, 1936–1947.

Montague, P. R., Hyman, S. E., & Cohen, J. D. (2004). Computational roles for dopamine in behavioural control. *Nature*, *431*, 760–767.

Morgan, A. B., & Lilienfeld, S. O. (2000). A meta-analytic review of the relation between antisocial behavior and neuropsychological measures of executive function. *Clinical Psychology Review*, *20*, 113–136.

Müri, R. M., Heid, O., Nirkko, A. C., Ozdoba, C., Felblinger, J., Schroth, G., & Hess, C. W. (1998). Functional organisation of saccades and antisaccades in the frontal lobe in humans: A study with echo planar functional magnetic resonance imaging. *Journal of Neurology, Neurosurgery & Psychiatry*, *65*, 374–377.

Nelson L. D., Strickland, C., Krueger, R. F., Arbisi, P. A., & Patrick, C. J. (2015). Neurobehavioral traits as transdiagnostic predictors of clinical problems. *Assessment*. doi: 10.1177/1073191115570110

Nelson, L. D., Patrick, C. J., & Bernat, E. M. (2011). Operationalizing proneness to externalizing psychopathology as a multivariate psychophysiological phenotype. *Psychophysiology*, *48*, 64–72.

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision-making, the P3, and the locus coeruleus-nonepinephrine system. *Psychological Bulletin*, *131*, 510–532.

Nigg, J. T., & Casey, B. J. (2005). An integrative theory of attention-deficit hyperactivity disorder based on the cognitive and affective neurosciences. *Development and Psychopathology*, *17*, 785–806.

Norman, A. L., Pulido, C., Squeglia, L. M., Spadoni, A. D., Paulus, M. P., & Tapert, S. F. (2011). Neural activation during inhibition predicts initiation of substance use in adolescence. *Drug and Alcohol Dependence*, *119*, 216–223.

Ochsner, K., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., & Gross, J. J. (2004). For better or for worse: Neural systems supporting the cognitive down–and up-regulation of negative emotion. *Neuroimage*, *23*, 483–499.

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. (2002). Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, *14*, 1215–1229.

Ogilvie, J. M., Stewart, A. L., Chan, R. C. K., & Shum, D. H. K. (2011). Neuropsychological measures of executive function and antisocial behavior: A meta-analysis. *Criminology*, *49*, 1063–1107.

Öhman, A. (1993). Fear and anxiety as emotional phenomena: Clinical phenomenology, evolutionary perspectives, and information processing mechanisms. In M. Lewis & J. M. Haviland (Eds.), *Handbook of emotions* (pp. 511–536). New York: Guilford.

Olds, J. (1956). Pleasure centers in the brain. *Scientific American*, *195*, 105–116.

Olds, J., & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology*, *47*, 419–427.

Olson, L. A. (2014). *Rapid affective processing event-related potentials and externalizing psychopathology correlates*. Unpublished dissertation, Florida State University at Tallahassee.

Pailing, P. E., & Segalowitz, S. J. (2004). The error-related negativity as a state and trait measure: Motivation, personality, and ERPs in response to errors. *Psychophysiology*, *41*, 84–95.

Patrick, C. J., & Bernat, E. M. (2009). From markers to mechanisms: Using psychophysiological measures to elucidate basic processes underlying aggressive externalizing behavior. In S. Hodgins, E. Viding, & A. Plodowski (Eds.), *Persistent violent offenders: Neuroscience and rehabilitation* (pp. 223–250). London: Oxford University Press.

Patrick, C. J., Bernat, E. M., Malone, S. M., Iacono, W. G., Krueger, R. F., & McGue, M. (2006). P300 amplitude as an indicator of externalizing in adolescent males. *Psychophysiology*, *43*, 84–92.

Patrick, C. J., & Drislane, L. E. (2014). Triarchic model of psychopathy: Origins, operationalizations, and observed linkages with personality and general psychopathology. *Journal of Personality*. doi: 10.1111/jopy.12119

Patrick, C. J., Durbin, C. E., & Moser, J. S. (2012). Conceptualizing proneness to antisocial deviance in neurobehavioral terms. *Development and Psychopathology*, *24*, 1047–1071.

Patrick, C. J., Fowles, D. C., & Krueger, R. F. (2009). Triarchic conceptualization of psychopathy: Developmental origins of disinhibition, boldness, and meanness. *Development and Psychopathology*, *21*, 913–938.

Patrick, C. J., Hicks, B. M., Krueger, R. F., & Lang, A. R. (2005). Relations between psychopathy facets and externalizing in a criminal offender sample. *Journal of Personality Disorders*, *19*, 339–356.

Patrick, C. J., Kramer, M. D., Krueger, R. F., & Markon, K. E. (2013a). Optimizing efficiency of psychopathology assessment through quantitative modeling: Development of a brief form of the Externalizing Spectrum Inventory. *Psychological Assessment*, *25*, 1332–1348.

Patrick, C. J., Venables, N. C., Yancey, J. R., Hicks, B. M., Nelson, L. D., & Kramer, M. D. (2013b). A construct-network approach to bridging diagnostic and physiological domains: Application to assessment of externalizing psychopathology. *Journal of Abnormal Psychology*, *122*, 902–916.

Peterson, J. B., & Pihl, R. O. (1990). Information processing, neuropsychological function, and the inherited

predisposition to alcoholism. *Neuropsychology Review*, *1*, 343–369.

Petrides, M. (2000). Dissociable roles of mid-dorsolateral prefrontal and anterior inferotemporal cortex in visual working memory. *Journal of Neuroscience*, *20*, 7496–7503.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, *43*, 897–905.

Phillips, A. G. (1984). Brain reward circuitry: A case for separate systems. *Brain Research Bulletin*, *12*, 195–201.

Poceta, S. J., Houser, M., & Polich, J. (2006). Event-related potentials in restless legs syndrome and Parkinson's Disease. *Sleep*, *28*, A274.

Polich, J. (2007). Updating the P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology*, *118*, 2128–2148.

Ponzi, C. (1934). Cited in M. Zuckoff (2006). *Ponzi's scheme: The true story of a financial legend* (p. 309). New York: Random House.

Quirk, G. J., Russo, G. K., Barron, J. L., & Lebron, K. (2000). The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *Journal of Neuroscience*, *20*, 6225–6231.

Raine, A., Ishikawa, S. S., Arce, E., Lencz, T., Knuth, K. H., Bihrle, S., . . . Colletti, P. (2004). Hippocampal structural asymmetry in unsuccessful psychopaths. *Biological Psychiatry*, *55*, 185–191.

Roberts, A. C., Robins, T. W., & Weiskrantz, L. (1998). *The prefrontal cortex: Executive and cognitive functions*. Oxford: Oxford University Press.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research Reviews*, *18*, 247–291.

Robinson, T. E., & Berridge, K. C. (2000). The psychology and neurobiology of addiction: An incentive-sensitization view. *Addiction*, *95*, S91–S117.

Robinson, T. E., & Berridge, K. C. (2003). Addiction. *Annual Review of Psychology*, *54*, 25–53.

Roca, P., Mulas, F., Presentación-Herrero, M. J., Ortiz-Sánchez, P., Idiazábal-Alecha, M. A., & Miranda-Casas A. (2012). Cognitive evoked potentials and executive functions in children with attention deficit hyperactivity disorder. *Revue Neurologique*, 54(Suppl. 1), S95–S103.

Rolls, E. T. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex*, *10*, 284–294.

Rubia, K., Smith, A., Halari, R., Matukura, F., Mohammad, M., Taylor, E., & Brammer, M. J. (2009). Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure attention-deficit/hyperactivity disorder during sustained attention. *American Journal of Psychiatry*, *166*, 83–94.

Saccone, S. F., Hinrichs, A. L., Saccone, N. L., Chase, G. A., Konvicka, K., Madden, P. A., . . . Bierut, L. J. (2007). Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Human Molecular Genetics*, *16*, 36–49.

Scheffers, M. K., Coles, M. G., Bernstein, P., Gehring, W. J., & Donchin, E. (1996). Event-related brain potentials and error-related processing: An analysis of incorrect responses to go and no-go stimuli. *Psychophysiology*, *33*, 42–53.

Salmi, J., Huotilainen, M., Pakarinen, S., Siren, T., Alho, K., & Aronen, E. T. (2005). Does sleep quality affect involuntary attention switching system? *Neuroscience Letters*, *390*, 150–155.

Sangal, R. B., & Sangal, J. M. (1997). Measurement of P300 and sleep characteristics in patients with hypersomnia: Do P300 latencies, P300 amplitudes, and multiple sleep latency and maintenance of wakefulness tests measure different factors? *Clinical Electroencephalography*, *28*, 179–184.

Sauder, C. L., Derbidge, C. M., & Beauchaine, T. P. (in press). Neural responses to monetary incentives among self-injuring adolescent girls. *Development and Psychopathology*.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, *80*, 1–27.

Schultz, W., Apicella, P., & Ljungberg, T. (1993). Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *Journal of Neuroscience*, *13*, 900–913.

Shen, Y. C., Fan, J. H., Edenberg, H. J., Li, T. K., Cui, Y. H., Wang, Y. F., . . . Xia, G. Y. (1997). Polymorphism of ADH and ALDH genes among four ethnic groups in China and effects upon the risk for alcoholism. *Alcoholism: Clinical and Experimental Research*, *21*, 1272–1277.

Sher, K. J., & Trull, T. J. (1994). Personality and disinhibitory psychopathology: Alcoholism and antisocial personality disorder. *Journal of Abnormal Psychology*, *103*, 92–102.

Shizgal, P. (1999). On the neural computation of utility: Implications from studies of brain stimulation reward. In D. Kahneman, E. Diener, & N. Schwarz (Eds.), *Well-being: The foundations of hedonic psychology* (pp. 500–524). New York: Sage.

Soderstrom, H., Tullberg, M., Wikkelsoe, C., Ekholm, S., & Forsman, A. (2000). Reduced regional cerebral blood flow in non-psychotic violent offenders. *Psychiatry Research: Neuroimaging*, *98*, 29–41.

Tarter, R. E. Alterman, A. I., & Edwards K. L. (1985). Vulnerability to alcoholism in men: A behavior-genetic perspective. *Journal of Studies on Alcohol*, *46*, 329–356.

Tellegen, A., & Waller, N. G. (2008). Exploring personality through test construction: Development of the Multidimensional Personality Questionnaire. In G. J. Boyle, G. Matthews, & D. H. Saklofske (Eds.), *The Sage handbook of personality theory and assessment* (vol. 2, pp. 261–292). Minneapolis: University of Minnesota Press.

Trenkwalder, C., & Winkelmann, J. (2003). Pathophysiology of the restless legs syndrome. In S. Chokroverty, W. A. Hening, & A. S. Walters (Eds.), *Sleep and movement disorders* (pp. 322–332). Philadelphia: Butterworth/Henemann.

Vaidyanathan, U., Patrick, C. J., & Iacono, W. G. (2011). Patterns of comorbidity among mental disorders: A person-centered approach. *Comprehensive Psychiatry*, *52*, 527–535.

Van der Oord, S., Prins, P. J. M., Oosterlaan, J., & Emmelkamp, P. M. G. (2008). Efficacy of methylphenidate, psychosocial treatments and their combination in school-aged children with ADHD: A meta-analysis. *Clinical Psychology Review*, *28*, 783–800.

Vanyukov, M. M., Kirisci, L., Moss, L., Tarter, R. E., Reynolds, M. D., Maher, B. S., . . . Clark, D. B. (2009). Measurement of the risk for substance use disorders: Phenotypic and genetic analysis of an index of common liability. *Behavior Genetics*, *39*, 233–244.

Vanyukov, M. M., Kirisci, L., Tarter, R. E., Simkevitz, H. F., Kirillova, G. P., Maher, B. S., & Clark, D. B. (2003). Liability to substance use disorders: 2. A measurement approach. *Neuroscience and Biobehavioral Reviews*, *27*, 517–526.

Vanyukov, M. M., Tarter, R. E., Kirillova, G. P., Kirisci, L., Reynolds, M. D., Kreek, M. J., . . . Ridenour, T. A. (2012). Common liability to addiction and "gateway hypothesis": Theoretical, empirical and evolutionary perspective. *Drug and Alcohol Dependence*, 123*S*, S3–S17.

Venables, N. C., & Patrick, C. J. (2012). Validity of the Externalizing Spectrum Inventory in a criminal offender sample: Relations with disinhibitory psychopathology, personality, and psychopathic features. *Psychological Assessment*, *24*, 88–100.

Verbaten, M. N., Overtoom, C. C., Koelga, H. S., Swaab-Barneveld, H., van der Gaag, R. T., Buitelaar, J., & van Engeland, H. (1994). Methylphenidate influences on both early and late ERP waves of ADHD children in a continuous performance test. *Journal of Abnormal Child Psychology*, *22*, 561–578.

Verona, E., & Patrick, C. J. (2015). Psychobiological aspects of antisocial personality disorder, psychopathy, and violence. *Psychiatric Times*. http://www.psychiatrictimes.com/special-reports/psychobiological- aspects-antisocial-personality-disorder-psychopathy-and-violence

Viding, E., Blair, R. J. R., Moffitt, T. E., & Plomin, R. (2005). Evidence for substantial genetic risk for psychopathy in 7-year-olds. *Journal of Child Psychology and Psychiatry*, *46*, 592–597.

Volkow, N. D., Fowler, J. S., & Wang, G. J. (2004). The addicted human brain viewed in light of imaging studies: Brain circuits and treatment strategies. *Neuropharmacology*, *47*, 3–13.

Volkow, N. D., Wang, G. -J., Fowler, J. S., & Tomasi, D. (2012). Addiction circuitry in the human brain. *Annual Review of Pharmacology and Toxicology*, *52*, 321–336.

Wagar, B. M., & Thagard, P. (2004). Spiking Phineas Gage: A neurocomputational theory of cognitive-affective integration in decision-making. *Psychological Review*, *111*, 67–79.

Wang, L., Kuroiwa, Y., & Kamitani, T. (1999). Visual event-related potential changes at two different tasks in nondemented Parkinson's disease. *Journal of Neurological Sciences*, *164*, 139–147.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience*, *18*, 411–418.

Wise, R. A. (1985). The anhedonia hypothesis: Mark III. *Behavioral and Brain Sciences*, *8*, 178–186.

Wise, S. P., Murray, E. A., & Gerfen, C. R. (1996). The frontal-basal ganglia system in primates. *Critical Reviews in Neurobiology*, *10*, 317–356.

Yancey, J. R., Venables, N. C., Hicks, B. M., & Patrick, C. J. (2013). Evidence for a heritable brain basis to deviance-promoting deficits in self-control. *Journal of Criminal Justice*, *41*, 309–317.

Young, S. E., Friedman, N. P., Miyake, A., Willcutt, E. G., Corley, R. P., Haberstick, B. C., & Hewitt, J. K. (2009). Behavioral disinhibition: Liability for externalizing spectrum disorders and its genetic and environmental relation to response inhibition across adolescence. *Journal of Abnormal Psychology*, *118*, 117–130.

Young, S. E., Stallings, M. C., Corley, R. P., Krauter, K. S., & Hewitt, J. K. (2000). Genetic and environmental influences on behavioral disinhibition. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, *96*, 684–695.

Zisner & Beauchaine. (this volume). Midbrain neural mechanisms of trait impulsivity. In T. P Beauchaine & S. P. Hinshaw (Eds.), *The Oxford handbook of externalizing spectrum disorders*. New York: Oxford University Press.