Patrick, C. J., & Bernat, E. M. (2010). Neuroscientific foundations of psychopathology. In T. Millon, R.F. Krueger, & E. Simonsen (Eds.), *Contemporary directions in psychopathology: Scientific foundations of the DSM-V and ICD-11* (pp. 419-452). New York: The Guilford Press.

CHAPTER 22

Neuroscientific Foundations of Psychopathology

CHRISTOPHER J. PATRICK
EDWARD M. BERNAT

Prominent scholars in the mental health field have called for efforts to integrate neurobiological concepts and findings directly into systems for diagnosing psychopathological disorders (Hyman, 2007), in order to improve the effectiveness of assessment, prevention, and treatment of such disorders (Insel & Scolnick, 2006). However, a number of challenges exist to understanding traditional mental disorders in neuroscientific terms. One of the most significant is that mental disorder syndromes represent complex targets for neurobiological study: They manifest themselves in diverse ways clinically (phenotypically), and they show frequent overlap (comorbidity) rather than occurring in isolation from one another. A further challenge is the essential measurement gap that exists between diagnostic phenotypes (operationalized in the domain of interview or self-report) and neurobiological systems/processes (operationalized in the domain of brain or other physiological activity). Yet another has to do with the psychometric limitations of single-session/single-task neuroscience procedures as a basis for *individual differences* assessment (Vul, Harris, Winkielman, & Pashler, 2009).

Here we propose that neuroscientific conceptualization and understanding of mental disorders can be advanced by focusing programmatic efforts on *neurobehavioral trait* constructs—that is, individual difference constructs with direct referents in neurobiology as well as behavior (Depue & Iacono, 1989). As concrete examples, we highlight fear–fearlessness and inhibitory control as two neurobehavioral constructs of relevance to differing forms of psychopathology. Variations in fear and fearlessness are posited to reflect individual differences in the sensitivity of the brain's defensive motivational system. Variations in inhibitory control are posited to reflect individual differences in the functioning of brain systems that modulate affective and behavioral response in the service of distal goals. We propose that these constructs, because they provide a concrete basis for linking neurobiological systems to measurable deviations in behavior, can serve as important initial referents for a "psychoneurometric" approach to the

assessment of individual differences relevant to psychopathology.

Psychometric and Experimental Approaches to the Study of Psychopathology

Two approaches to the neurobiological study of mental disorders have predominated for many years up to the present. One is the psychometric–dimensional approach, which relies on correlational analytic methods; the other is the experimental–diagnostic approach, which relies on statistical comparisons of groups. The former—exemplified by the work of such writers as Eysenck (1967), Tellegen (1985), and Cloninger (1987)—entails efforts to identify psychopathology-related individual difference dimensions on the basis of quantitative/psychometric methods and link them to neurobiological systems and processes. The latter—exemplified by the work of early experimental psychopathologists like Hare (1978), Lykken (1957), Maher (1968), and McGhie and Chapman (1961), as well as that of many contemporary clinical neuroscientists (e.g., Barch et al., 2001; Blair, 2006; Gotlib et al., 2005; Heller, Nitschke, Etienne, & Miller, 1997)—entails efforts to identify neurobiological processing or reactivity differences between participant groups classified on the basis of the presence versus absence of some diagnostic condition.

Although each of these approaches has contributed importantly to our understanding of neurobiological factors in psychopathology, notable limitations are associated with each. Research in the psychometric–dimensional tradition has for the most part focused on personality trait constructs defined on the basis of self-report. This approach is advantageous in that it makes use of specialized quantitative methods (including item analysis, structural analysis, and varying types of reliability analysis) to optimize precision and consistency of measurement of target individual difference dimensions. In addition, it provides for efficient data collection with high numbers of participants. As a function of these advantages, research employing the psychometric–dimensional approach has yielded robust and replicable findings in large participant samples. However, the trait constructs targeted in work of this sort, although associated empirically with psychopathological syndromes, do not converge clearly with specific diagnostic conditions (i.e., they correlate to varying degrees, and moderately at best, with multiple disorders).

In contrast, experimental psychopathology research has focused predominantly on diagnostic conditions of interest, including those defined within the current version (fourth edition, text revision) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR; American Psychiatric Association, 2000). The power of this approach derives from the elegance of experimental task paradigms that can be brought to bear on the study of psychopathology. Contemporary clinical neuroscience research, for example, combines the methodological sophistication of cognitive science with the precise anatomical measurement afforded by techniques such as dense-array electroencephalography (EEG), magnetoencephalography (MEG), and magnetic resonance imaging (MRI) to elucidate brain-based processing differences associated with psychopathological syndromes. However, a common limitation of studies of this type, because of the greater time and costs associated with recruitment and experimental testing of patients, is that sample sizes tend to be small and effects tend to be of varying stability. A further, more fundamental limitation to this approach is that it is in fact *quasi*-experimental by nature (cf. Campbell & Stanley, 1966), rather than truly experimental. That is, groups selected to differ in the presence versus absence of a designated diagnostic condition can easily differ in ways that are either distinct from, or not specific to, that condition—such that group differences on experimental measures may reflect variables other than the presence of the condition per se. A common means of controlling for condition-irrelevant confounds is to match groups on such variables as gender, age, and patient status. Along similar lines, the problem of diagnostic effect specificity is commonly dealt with by selection of "pure cases"—that is, individuals possessing only the disorder of interest without co-occurring psychopathology. However, truly "pure" cases (i.e., lacking even subthreshold comorbid conditions) are rare in patient populations and thus unrep-

resentative of cases that come to the attention of clinicians. Related to this, pure cases commonly represent weaker variants of the condition of interest, in terms of severity and chronicity of symptoms—variants in which core neurobiological diatheses may play a lesser etiological role.

A further crucial limitation of both the psychometric–dimensional and the experimental–diagnostic approaches to the neurobiology of psychopathology is that the individual difference (phenotypic) constructs of interest in each case are not directly biological. In the case of the psychometric–dimensional approach, systematic efforts are made to precisely operationalize psychologically oriented individual difference constructs on the basis of self-report items, followed by efforts to map their neurobiological correlates. In some work, individual difference constructs are selected that have neurobiological as well as psychological referents (e.g., Cloninger, 1987; Depue, Luciana, Arbisi, Collins, & Leon, 1994; Gray, 1991); even in work of this kind, however, target phenotypes are operationalized on the basis of nonbiological, self-report-based indicators. Observed correlations between specific psychometric phenotypes and relevant physiological indicators in large samples, although robust, are typically small in magnitude (.30 or lower; e.g., Benning, Patrick, & Iacono, 2005; Hall, Bernat, & Patrick, 2007). This is true for at least three essential reasons. The first is that self-report assessment and physiological response assessment reflect different domains of measurement. As noted many years ago by Campbell and Fiske (1959), indicators of the *same construct* derived from differing measurement domains are expected to correlate only moderately (.30–.60), at best. A second reason is that physiological variables in studies of this type are typically linked too loosely to psychometric trait variables of interest to be considered indicators of the same construct. This further constrains the observed relations between variables across the two domains. Third, whereas self-report trait measures are normally developed through an iterative process of item generation, administration, evaluation, and refinement that results in a final set of indicators with demonstrable reliability for indexing a specified target construct, no such process is typically employed with physiological measures in order to establish their reliability as individual difference measures per se—much less their reliability as indicators of *specified* psychological trait constructs.

In the experimental–diagnostic approach, on the other hand, systematic effort is devoted to precisely operationalizing psychologically meaningful processes on the basis of carefully designed behavioral tasks, followed by application of these tasks to identify processing differences associated with nonbiologically defined phenotypic categories (i.e., diagnostic groups). In clinical neuroscience studies, dependent variables of interest consist of direct brain response measures, including measures such as blood-oxygen-level-dependent (BOLD) MRI that yield precise information regarding anatomical sites of neural activity. However, a number of factors limit the sensitivity and specificity of physiological measures (including direct brain response measures) within isolated tasks as indicators of neural processes relevant to particular diagnostic conditions. Some of these factors mirror those described above in relation to neurobiological studies of self-report trait constructs: Diagnostic and physiological assessments reflect differing measurement domains; constructs tapped by brain response indices in experimental tasks do not directly match constructs tapped by diagnostic symptom indicators; and experimental task paradigms are normally developed for the purpose of operationalizing *normative* psychological processes of interest, without systematic effort devoted to ensuring their effectiveness as *individual difference* measures.

In addition, the experimental–diagnostic approach has some distinctive limitations as a method for elucidating neurobiological factors in psychopathological conditions. One is that diagnostic classification is a dichotomous approach to phenotyping that does not take into account variations in symptom expression or severity. Participants categorized as meeting criteria for a diagnosis can exhibit varying numbers and types of symptoms, with severity of particular symptoms varying from one participant to another, and individuals classified as not meeting criteria for a diagnosis can nonetheless vary in degree of (subthreshold) symptomatology. Furthermore, the pervasive phenomenon of

diagnostic comorbidity ensures that participants meeting criteria for a particular clinical disorder will routinely exhibit symptoms of other disorders as well as features specific to the disorder of interest. In addition, much of this comorbidity is systematic rather than random (i.e., particular disorders co-occur more frequently with disorders of certain types than with others; cf. Krueger, 1999b). As discussed below, the implication is that various disorders share underlying processing deviations in common. As a function of this, group differences in brain (or other physiological) reactivity observed in experimental–diagnostic studies may reflect processes common to disorders of differing types more than they do processes specific to the target disorder of interest.

In summary, both the psychometric–dimensional and the experimental–diagnostic approaches—while informative, respectively, about individual difference dimensions affiliated with varying forms of psychopathology, and underlying processes implicated in disorders of particular types—are nonetheless limited as methods for mapping deviations in the function of particular neurobiological systems onto disorder-relevant phenotypes. In particular, with each of these approaches, a substantial measurement gap exists between phenotypes of interest (either trait constructs or diagnostic categories) and neurobiological systems/processes of interest. As a complement to these existing approaches, directed toward bridging the gap between psychopathological phenotypes and biological systems, we highlight in this chapter a third potential approach we term the "psychoneurometric" approach. Psychoneurometrics can be defined as the systematic development of neurobiologically based trait measures, using psychological (psychometric) phenotypes as referents.

As applied to the study of mental disorders, the goal of this approach is to establish direct *neurophysiological* measures of individual difference constructs relevant to psychopathology that have optimal psychometric properties. Rather than targeting trait constructs from particular models of personality, or discrete diagnostic entities (e.g., as defined in the DSM), the psychoneurometric approach targets relevant neurobehavioral trait constructs (i.e., trait constructs with direct referents in neurobiology as well as behavior). Established psychometric measures of these target constructs serve as initial referents for the identification of reliable indicators in the physiological domain. As illustrated and discussed later (see "Toward a Psychoneurometrics of Psychopathology," below), observed convergences among differing neurophysiological indicators can provide insights into the nature of brain variations relevant to individual difference constructs of interest. This information in turn can be used to refine psychological conceptualizations (and psychometric operationalizations) of these target constructs—and psychopathological conditions with which they are associated.

This chapter focuses on two neurobehavioral constructs in particular: defensive reactivity and inhibitory control. We focus on these constructs because of their demonstrable relevance to differing forms of psychopathology in DSM (Axis II personality syndromes as well as Axis I clinical disorders), and because empirical demonstrations are available of how these constructs can be indexed physiologically as well as behaviorally/psychometrically. The next section below highlights the phenomenon of comorbidity and describes integrative hierarchical models that have been developed to account for this phenomenon in terms of broad factors that disorders share, while at the same time positing distinct lower-order factors that account for unique features of individual disorders. Considering the emphasis assigned to abnormal emotional response and deficient impulse control in the definitions of many different mental disorders, our view is that constructs of defensive reactivity and inhibitory control are particularly relevant to an understanding of processing deviations that differing disorders have in common. The third major section below discusses psychological conceptualizations of defensive reactivity and inhibitory control, highlighting specialized psychometric measures of dispositional fear/fearlessness and disinhibitory (externalizing) tendencies. The fourth section reviews neurobiological conceptualizations of defensive reactivity and inhibitory control (i.e., brain systems relevant to these individual difference constructs) and summarizes evidence regarding neurophysiological correlates of these constructs. The

fifth section describes empirical data linking the constructs of defensive reactivity and inhibitory control, operationalized as dispositional fear and externalizing proneness, to differing forms of psychopathology (Axis II as well as Axis I) within DSM. The sixth section provides an illustration of the psychoneurometric approach, drawing on multiple known electrocortical indicators of externalizing tendencies. The chapter ends with a brief discussion of implications for future research.

Accounting for Comorbidity among Mental Disorders: Hierarchial Models

The classic medical perspective on psychopathology, which served as the foundation for the DSM nosological system, is that individual diagnostic syndromes represent discrete phenotypic entities with distinctive etiological underpinnings. However, a significant challenge to operationalizing mental disorders in this fashion is the well-documented phenomenon of diagnostic comorbidity (e.g., Clark, Watson, & Reynolds, 1995; Kendler, Prescott, Myers, & Neale, 2003; Krueger, 1999b; Vollebergh et al., 2001; Zuckerman, 1999). That is, mental disorders tend not to occur in isolation from one another; rather, they occur more typically in overlapping fashion within the same individual. For example, individuals diagnosed with major depression often exhibit co-occurring anxiety disorders (e.g., social phobia, panic disorder), as well as fearful/anxious personality disorders (e.g., avoidant, dependent). As noted earlier, one reason why the phenomenon of comorbidity poses a significant challenge to neurobiological research on the mechanisms of psychopathology is that in research on particular disorders of interest, it is possible that the etiological process under investigation may be generally characteristic of that disorder as well as others that reliably co-occur with it, rather than specific to the disorder of interest. A second reason is that comorbidity is so prevalent that "pure-case" research (i.e., research focusing on non-comorbid cases of a specific disorder) is likely to be unrepresentative of clinical cases encountered in practice and thus limited in generalizability.

A valuable approach to accommodating the phenomenon of diagnostic comorbidity has been to develop hierarchical models encompassing particular families (spectra) of interrelated mental disorders. These models account for the comorbidity among differing syndromes in terms of a broad factor reflecting their shared variance (overlapping symptomatology), along with specific factors reflecting the unique variance (distinct symptomatology) of particular disorders. From an etiological standpoint, the broad factor can be viewed as reflecting common etiological influences that contribute to all disorders within a spectrum, whereas specific factors reflect narrower etiological influences that determine the unique symptomatic expression of particular disorders. Models of this sort have been developed for anxiety and mood ("internalizing") disorders, and for impulse control ("externalizing") disorders.

In the domain of internalizing psychopathology, Mineka, Watson, and Clark (1998) proposed a hierarchical model in which unipolar depression and various anxiety-related disorders share a common broad factor of "negative affect" (NA), reflecting general distress, susceptibility to negative mood states, and hypervigilance to threat. In addition, Mineka et al. postulated that each individual internalizing disorder has a specific etiological factor accounting for its uniqueness. For example, although depression (like the various anxiety disorders) is associated with heightened NA, it is distinguished by a reduced capacity for pleasurable mood states. Among the anxiety disorders, panic disorder is distinguished from the others by the presence of physiological hyperreactivity ("anxious arousal"), manifested in the form of acute panic attacks.

In a revision of this model, Watson (2005) proposed a nosological distinction between "distress" disorders (comprising major depression, dysthymic disorder, generalized anxiety disorder, and posttraumatic stress disorder [PTSD]) and "fear" disorders (encompassing specific phobia, social phobia, panic disorder, and agoraphobia). This distinction was inspired importantly by Krueger's (1999b) demonstration of separable "anxious misery" versus "fear" disorder subcategories within the internalizing spectrum. In Watson's revised model, these two

subcategories have in common an overarching NA (general subjective distress) factor, but (1) this broad factor accounts for substantially more variance in the distress disorders than in the fear disorders; and (2) the fear disorders are distinguished by the presence of salient physiological hyperarousal (uncued negative activation, in the case of panic disorder; situationally bound negative activation, in the case of the phobic disorders). Relevant to this conceptualization, Sellbom, Ben-Porath, and Bagby (2008) parsed the broad construct of NA into distinctive (albeit correlated) "demoralization" and "dysfunctional negative emotion" components, reflecting general dysphoria/dissatisfaction/helplessness and negative emotional activation, respectively. They demonstrated that demoralization was more strongly characteristic of distress disorders, whereas high negative activation was more strongly characteristic of fear disorders. These authors also reported distinctive associations of low positive affect with major depression (within the distress disorder category) and social phobia (within the fear disorder category).

In the domain of externalizing psychopathology, Krueger and colleagues (2002) demonstrated, in a sample of twins, the existence of a general "externalizing" factor accounting for the shared variance among diverse impulse control disorders within DSM (i.e., child conduct disorder, adult antisocial behavior, alcohol dependence, and drug dependence), along with scores on a self-report measure of disinhibitory personality. These authors estimated that over 80% of the variance in this common externalizing factor was attributable to additive genetic influence (see also Kendler et al., 2003; Young, Stallings, Corley, Krauter, & Hewitt, 2000). In contrast, the residual variance in each of the diagnostic variables as well as the personality variable not accounted for by the broad externalizing factor was accounted for mainly by nonshared environmental influence (with shared environment also contributing specifically to conduct disorder). Krueger and colleagues proposed a hierarchical model based on these findings, in which the general externalizing factor represents a predominantly heritable vulnerability that contributes to the development of diverse traits and problem behaviors, with the precise phenotypic expression of this vulnerability (i.e., as subclinical disinhibitory tendencies, antisocial deviance of different sorts, or alcohol or drug problems) determined by other, more specific etiological influences. Krueger, Markon, Patrick, Benning, and Kramer (2007) extended this work by developing a comprehensive quantitative–hierarchical model to accommodate a broad spectrum of impulse control problems and traits, operationalized as coherent lower-order constructs in the domain of self-report. As described further in the next section below, this work corroborated the existence of an overarching externalizing factor accounting for substantial variance in all traits and problems within this spectrum, and also revealed evidence of distinct subordinate factors (callous aggression, addiction proneness) accounting for residual variance in particular subsets of traits/problems.

These hierarchical models are valuable because they point to a novel two-part strategy for investigating etiological contributions to mental disorders. One part entails studying the nature and bases of broader individual difference factors that contribute to varying disorders within a spectrum (i.e., generalized distress, physiological hyperreactivity, and diminished positive affect in the case of internalizing disorders; general externalizing tendencies, callousness, and addiction proneness in the case of externalizing disorders). This component is essential for dealing with the phenomenon of diagnostic comorbidity—in particular, for differentiating processes that are common to varying disorders from those that are unique to individual disorders. The other part involves studying the aspects of each individual disorder that distinguish it from affiliated disorders within a spectrum. This component is essential to understanding unique influences contributing to the development and maintenance of particular disorders. For example, panic disorder can be understood in part through investigation of factors contributing to generalized distress (which is common to all internalizing disorders) and to physiological hyperreactivity (which is more specific to fear disorders), but also through investigation of unique aspects of panic disorder (e.g., its lack of cue specificity). Studies along these lines can be conducted by using quantitative/statistical methods (e.g., structural modeling) to partition individual

disorders into their broad versus distinctive facets, or by using a case-based strategy in which groups are selected to exemplify one or the other another facet (e.g., individuals with symptoms of differing impulse control disorders can be selected for studies of the etiology of the general externalizing factor; individuals meeting criteria for a single disorder but low on the general externalizing factor can be selected for studies of unique etiological influences contributing to that disorder).

Notably, these hierarchical models have been developed and refined primarily on the basis of diagnostic symptom data and self-report questionnaire measures. Although the broad factors described in these models are presumed to have neurobiological referents (linked to temperament dispositions; see e.g., Clark & Watson, 1999; Patrick & Bernat, 2006), these referents have yet to be elucidated. A primary aim of the current chapter is to summarize empirical evidence linking differing forms of psychopathology (and, in particular, the factors they share) to two individual difference constructs with direct neurobiological as well as behavioral referents: defensive reactivity and inhibitory control. Individual differences in defensive (fear) reactivity are conceptualized as reflecting variations in the sensitivity of the brain's defensive motivational system. The psychometric–dimensional phenotype corresponding to defensive reactivity has been labeled "dispositional fear–fearlessness" or "trait fear" (Kramer, Patrick, Krueger, & Bayevsky, 2010; Patrick & Bernat, 2009b; Vaidyanathan, Patrick, & Bernat, 2009). Individual differences in inhibitory control are posited to reflect variations in the functioning of brain systems that operate to guide and inhibit behavior and to regulate affective response in the service of distal goals. The psychometric–dimensional phenotype corresponding to this dispositional construct has been labeled "disinhibition" (Patrick, Fowles, & Krueger, 2009; Patterson & Newman, 1993; Sher & Trull, 1994) or "externalizing" (Achenbach & Edelbrock, 1978; Krueger et al., 2002; Krueger, Markon, et al., 2007). The sections that follow describe how the individual difference constructs of defensive reactivity and inhibitory control can be conceptualized in psychological and neurobiological terms, and how these constructs relate to varying forms of psychopathology.

Psychological Conceptualizations of Defensive Reactivity and Inhibitory Control

Defensive (Fear) Reactivity

The emotional state of fear has been conceptualized in terms of reactivity of the brain's defensive motivational system, which functions to prime evasive action in the presence of threat cues (Davis, 1992; Fanselow, 1994; Lang, 1995; LeDoux, 1995). The idea of biologically based differences in general fearfulness is plausible from a biological–evolutionary perspective, insofar as tendencies toward greater versus lesser defensive reactivity have differing adaptive value across varying environmental contexts (owing to such factors as resource availability and prevalence of dangers; cf. Lykken, 1995). Individual differences in fear have been featured prominently in theories of temperament and personality. Goldsmith and Campos (1982) posited fearfulness as one of five basic dimensions of temperament, and Buss and Plomin (1984) identified fear as one of two basic trait expressions of negative emotional reactivity (the other being anger) that emerge within the first year of life. A scale assessing proneness to fear (Distress to Novelty) is included in Rothbart's (1981) widely used Infant Behavior Questionnaire (IBQ); Goldsmith, Lemery, Buss, and Campos (1999) examined etiological contributions to IBQ scale scores, and reported a prominent additive genetic contribution to this fear scale. Kochanska (1997) has emphasized variations in dispositional fear as an important moderator of conscience development in children. Timidity in novel situations is also central to Kagan's (1994) concept of inhibited temperament in children, which he views as a trait risk factor for the development of anxiety-related problems.

In the adult personality literature, a trait construct of "harm avoidance," reflecting avoidance of dangerous and unfamiliar situations, is represented in Tellegen's (1982) Multidimensional Personality Questionnaire (MPQ) and in Cloninger's (1987) Tridimensional Personality Questionnaire (TPQ).[1]

Trait fearlessness has also been addressed in the literatures on temperament and personality. For example, the counterpart to the inhibited child in Kagan's theory is the uninhibited or "low-reactive" child, described as nonfearful, venturous in novel situations, and socially assertive (Kagan, 1994; Kagan & Snidman, 1999). Fearlessness is also represented in Zuckerman's (1979) well-known Sensation Seeking Scale (SSS), in its Thrill and Adventure Seeking (TAS) subscale.

To refine conceptualization and psychometric measurement of defensive (fear) reactivity as a dispositional construct, and to examine its etiological foundations, Kramer and colleagues (2010) collected data for the following established fear and fearlessness scales in a large, mixed-gender sample (N = 2,572) of monozygotic and dizygotic twins recruited from the community: the Fear Survey Schedule (FSS; Arrindell, Emmelkamp, & van der Ende, 1984); the Fearfulness subscale of the Emotionality–Activity–Sociability Temperament Inventory (EAS-Fear; Buss & Plomin, 1984); the four subscales (Fear of Uncertainty, Shyness with Strangers, Anticipatory Worry, Fatigability) constituting the Harmavoidance (HA) scale of Cloninger's (1987) TPQ; the TAS subscale of Zuckerman's (1979) SSS; and the three subscales (Fearlessness, Stress Immunity, Social Potency) composing the Fearless Dominance (FD; Benning, Patrick, Hicks, Blonigen, & Krueger, 2003) factor of the Psychopathic Personality Inventory (PPI; Lilienfeld & Andrews, 1996). Confirmatory factor analyses of these various measures revealed the best fit for a model in which all scales loaded substantially on a general, overarching factor (labeled "trait fear"). Fearfulness measures (FSS, EAS-Fear, the four TPQ-HA subscales) loaded positively (M loading = +.69) on this factor, whereas fearlessness measures (the three PPI-FD scales, SSS-TAS) loaded negatively (M = –.58). Given the twin composition of the sample, it was possible to estimate genetic and environmental contributions to scores on this trait fear factor. Its estimated heritability (i.e., percentage of variance in scores attributable to genetic influence; Falconer, 1989) was 74%, with the remaining 26% attributable to nonshared environment. Thus the general disposition toward fear versus fearlessness indexed by these differing psychometric measures (like the broad externalizing factor identified by Krueger et al., 2002) constitutes a highly heritable phenotype.

Inhibitory Control

Psychological theorists since the earliest days of the discipline have recognized a broad dimension of human variation encompassing tendencies toward behavioral restraint versus disinhibition. In his classic *Principles of Psychology*, William James (1890/1983) noted that "there is a type of character in which impulses seem to discharge so promptly into movements that inhibitions get no time to arise" (p. 1144). Along these lines, contemporary theorists in the domains of personality and psychopathology have identified individual difference constructs ranging from "ego control" (Block & Block, 1980) to "constraint" (Tellegen, 1985) to "novelty seeking" (Cloninger, 1987) to "syndromes of disinhibition" (Gorenstein & Newman, 1980). The dimension of behavioral restraint versus impulsivity is also featured prominently in developmental theories of temperament (e.g., Buss & Plomin, 1975; Kochanska, 1997; Rothbart & Ahadi, 1994).

With regard to the psychological bases of impulse control problems, Patterson and Newman (1993) proposed a four-stage model of inhibitory processing to account for the impulsive behavior of disinhibited individuals. These authors posited that the processing deviation most germane to general disinhibitory tendencies (also known as "general proneness to externalizing"; Krueger et al., 2002; Krueger, Markon, et al., 2007) entails impairments at stages 3 and 4 of this model. Stage 3 represents the stage at which the occurrence of a conflictual event normally prompts a shift from an ongoing, goal-oriented response set to a passive, information-gathering set. According to Patterson and Newman, impairments at this processing stage have implications both for inhibition of immediate ongoing behavior at stage 3, and for the formation or strengthening of associative representations crucial to prospective reflection (i.e., inclination to anticipate potential consequences of one's actions) at stage 4. Patterson and Newman posited that this mechanism is crucial to an understanding of disinhibited behav-

ior associated with a variety of syndromes, including antisocial/psychopathic behavior, substance dependence (i.e., early-onset alcoholism), and attention-deficit/hyperactivity disorder (ADHD).

In an effort to refine psychometric measurement and conceptualization of inhibitory control as a dispositional construct, Krueger, Markon, and colleagues (2007) used traditional as well as more contemporary item-analytic methods (including item response modeling, exploratory factor analysis, and hierarchical cluster analysis) to develop a new self-report-based instrument, the Externalizing Spectrum Inventory (ESI), for comprehensively assessing the domain of externalizing problems and traits in terms of coherent lower-order constructs. The ESI includes 23 unidimensional scales developed to measure distinctive constructs, including varying forms of impulsiveness; differing types of aggression (physical, relational, and destructive); irresponsibility; rebelliousness; excitement seeking; blame externalization; and alcohol, drug, and marijuana use/problems. Confirmatory factor analyses of these 23 scales yielded evidence of a overarching factor (externalizing) on which all subscales loaded substantially (.45 or higher), and two subordinate factors (callous aggression, addictions) that accounted for residual variance in particular subscales. As noted earlier, these findings provide further support for the idea that a common dispositional factor (externalizing) contributes to a broad array of impulse control problems and affiliated traits. In addition, they suggest that separate dispositional factors shape the expression of externalizing tendencies toward callous aggression on the one hand, and addictive behaviors on the other.

Neurobiological Bases and Physiological Correlates

Defensive (Fear) Reactivity

As noted, the emotional state of fear is presumed to reflect activation of the brain's defensive motivational system. The amygdala in particular has been described as a core component of the defensive (fear) system in mammals (Davis, 1992; Fanselow, 1994; LeDoux, 1995). Research with adult human participants has demonstrated a role for genetic factors in individual differences in fear conditioning (Hettema, Anna, Neale, Kendler, & Fredrikson, 2003) and has revealed associations between specific gene alleles and variations in reactivity of the amygdala to fear stimuli (e.g., Harari et al., 2002). Young children exhibiting what Kagan has described as disinhibited temperament show reduced amygdala reactivity to novel human faces, when tested as adults, compared with individuals classified as inhibited (Schwartz, Wright, Shin, Kagan, & Rauch, 2003).

However, it is important to note that the amygdala represents only one element of the circuitry involved in defensive motivational processing and activation. For example, the bed nucleus of the stria terminalis shares close connections with the amygdala and has been hypothesized to form part of an extended amygdala system that governs more enduring (tonic) activation in relation to strong or persistent stressors (Davis, Walker, & Lee, 1997). The amygdala also interacts with higher brain regions that govern such processes as directed attention, declarative memory, and response inhibition (Davidson, Putnam, & Larson, 2000; LeDoux, 1995). Thus abnormal levels of negative emotional reactivity can reflect deviations in the functioning of other brain structures besides the amygdala (cf. Curtin, Patrick, Lang, Cacioppo, & Birbaumer, 2001; Patrick & Lang, 1999). Furthermore, the amygdala does not appear to function strictly as a fear activation system. There is evidence for its involvement in detecting unfamiliar stimuli more generally, in prioritizing attention to stimuli in the environment, and in activating positive as well as negative emotion (Lang, Bradley, & Cuthbert, 1997). Thus deviations in amygdala functioning may be associated with abnormalities in other types of processing aside from fear.

One methodology that has proven effective as an index of defensive reactivity to aversive stimuli is potentiation of the startle reflex to an intervening noise probe, measured via the eyeblink response in humans or via the whole-body "jump" reaction in animals. Davis and colleagues (e.g., Davis, 1989; Davis, Falls, Campeau, & Kim, 1993) mapped the neural circuitry of fear-potentiated startle in animals, establishing that the mechanism for this effect is a path-

way from the central nucleus of the amygdala to the nucleus reticularis pontis caudalis, the brainstem node of the basic startle circuit. In humans, the startle blink response to sudden noise is reliably enhanced during viewing of aversive pictures compared with neutral pictures (Lang, 1995; Lang, Bradley, & Cuthbert, 1990). Blink potentiation is strongest for directly threatening images (e.g., aimed weapons, menacing attackers), although it also occurs less reliably for vicarious aversive scenes involving physical injury or aggression (Bernat, Patrick, Benning, & Tellegen, 2006; Bradley, Codispoti, Cuthbert, & Lang, 2001; Levenston, Patrick, Bradley, & Lang, 2000). This effect in humans is blocked by diazepam (Patrick, Berthot, & Moore, 1996), a drug that inhibits activity in the amygdala, and that has also been shown to block fear-potentiated startle in animals (Davis, 1979).

There is also evidence for the specificity of aversive startle potentiation as an index of fear. Davis and colleagues (1997) presented evidence that fear-potentiated startle, associated with phasic (time-limited) increases in defensive activation tied to an explicit aversive cue, is mediated by the central nucleus of the amygdala, whereas startle reflex sensitization, associated with more tonic (prolonged) states of negative emotional activation, is mediated by the bed nucleus of the stria terminalis (BNST). From this standpoint, startle potentiation during discrete aversive cuing holds potential as a physiological indicator of individual differences in fear reactivity in humans. In this regard, increased startle potentiation during viewing of fear-relevant scenes has been demonstrated in individuals with phobic disorders (e.g., Hamm, Cuthbert, Globisch, & Vaitl, 1997; Vrana, Constantine, & Westman, 1992); and deficient fear-potentiated startle is reliably observed in incarcerated offenders diagnosed with psychopathy (cf. Patrick & Bernat, 2009b), a condition theorized to entail a deficiency in fear. In contrast with results for individuals with phobic fears, patients diagnosed with distress disorders such as depression and PTSD show normal fear-potentiated startle in relation to discrete aversive cues, but enhanced startle sensitization under conditions of prolonged stress or uncertainty (Grillon & Baas, 2003). The implication is that increased startle potentiation reflects heightened cue-specific defensive reactivity in individuals with phobic fear disorders, whereas enhanced startle sensitization reflects a more pervasive anxiety process (perhaps akin to high generalized NA; Watson, 2005) in individuals with distress disorders (cf. Davis et al., 1997; Rosen & Schulkin, 1998). Findings for panic disorder are more mixed: Although the general trend of evidence points to enhanced startle sensitization in clinic patients diagnosed with panic, rather than enhanced cue potentiation, the moderating role of comorbid distress disorders (e.g., depression, generalized anxiety) needs to be considered in studies employing patients seeking treatment for panic disorder. In this regard, a recent study by Melzig, Weike, Zimmermann, and Hamm (2007) found that patients with panic disorder but *without* comorbid depression, in relation to healthy controls, showed enhanced potentiation of startle during exposure to a threat cue; in contrast, patients with panic disorder *and* comorbid depression showed no such augmentation of threat-potentiated startle. These authors concluded that patients with panic but not depression respond like individuals with other fear disorders (e.g., specific or social phobia), whereas patients with panic and comorbid depression respond more like individuals with distress disorders.

Individual differences in startle reflex potentiation during aversive cuing have also been reported in relation to scores on differing psychometric scale measures of fear, fearlessness, and psychopathy—including the FSS (cf. Cook, 1999), the TPA-HA scale (Corr et al., 1995; Corr, Kumari, Wilson, Checkley, & Gray, 1997), the SSS-TA scale (Lissek & Powers, 2003), and the FD factor of the PPI (Benning, Patrick, Blonigen, Hicks, & Iacono, 2005). As noted earlier, these scale measures function as high- and low-pole indicators, respectively, of a common "trait fear" dimension (Kramer et al., 2010). Based on the known bivariate relations of these varying scale indicators with magnitude of aversive startle potentiation, Vaidyanathan and colleagues (2009) tested the hypothesis that aversive startle potentiation represents a continuous *physiological* indicator of this underlying trait fear dimension. Participants in this study were college men and women (N = 88) who were

administered the FSS, the EAS-Fear and SSS-TAS scales, and the subscales constituting the TPQ-HA and PPI-FD. Participants were tested in an affect–startle procedure that included differing categories of aversive (threat, physical injury, other-attack) and pleasant picture stimuli (erotic, action, nurturant) along with neutral pictures. Consistent with the findings of Kramer and colleagues (2010), a principal-components analysis of these various trait scales in this test sample yielded evidence of a dominant first factor on which all scales loaded substantially. An omnibus index of trait fear was computed for each participant, consisting of scores on the first component from this analysis. A modest but statistically robust linear relationship was found (in the sample as a whole, and for male and female subgroups separately) between trait fear and startle modulation for threat pictures in particular—the picture category, as noted earlier, that is most directly fear-relevant and yields the most reliable startle potentiation effects (see Figure 22.1). The findings of this study confirm that aversive startle potentiation represents a physiological indicator of the psychometric trait fear dimension, and lend support to the idea that these two variables (startle potentiation, trait fear) represent indices of a common neurobehavioral trait construct (i.e., reactivity of the defensive motivational system).

As discussed further in the final section below, multiple physiological indicators of trait fear will be required to establish a direct physiological index of individual differences in defensive reactivity with effective psychometric properties. Thus the demonstration of an association between aversive startle potentiation and trait fear represents only an initial step in this direction. To proceed further, systematic research will need to be undertaken to identify additional physiological indicators of trait fear. In this regard, the available literature suggests a variety of potential candidates. For example, another method that has been used to index

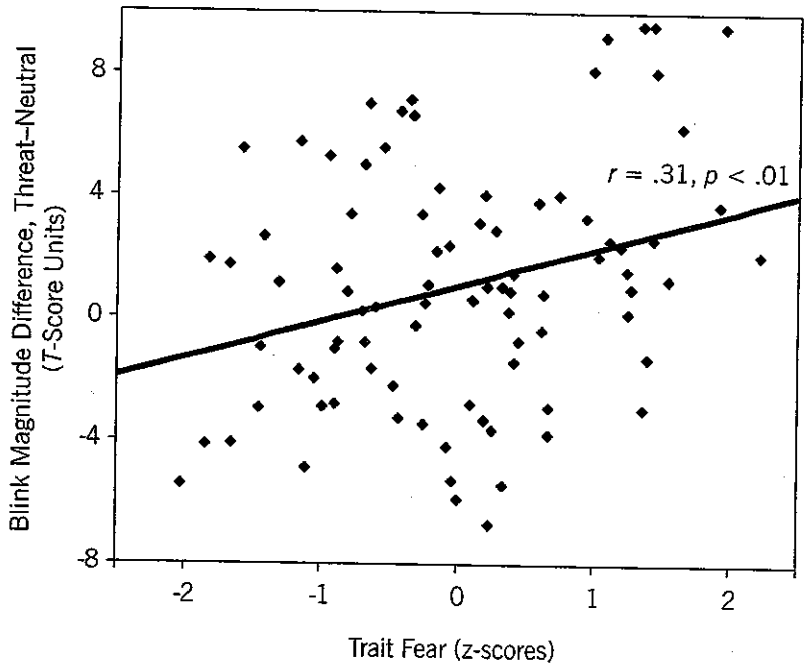

FIGURE 22.1. Scatterplot of the association, within a sample of male and female college students (N = 88), between trait fear scores and startle potentiation scores, defined as average magnitude of blink response to noise probes during viewing of direct-threat pictures (aimed weapons, menacing attackers) minus average magnitude of blink response during viewing of neutral pictures. Solid line is best-fitting regression line. Trait fear scores consist of scores on the first principal component derived from a principal-components analysis of varying self-report measures of fear and fearlessness. From Vaidyanathan, Patrick, and Bernat (2009). Copyright 2009 by Wiley-Blackwell. Reprinted by permission.

individual differences in fear and fearlessness involves measurement of responses to affective face stimuli. There is evidence that emotional facial expressions (fearful expressions in particular) reliably activate the amygdala in humans (e.g., Morris et al., 1996; Whalen, 1998), and that individuals high in NA show increased amygdala reactivity to fear faces (e.g., Bishop, Duncan, & Lawrence, 2004). There is also evidence that individuals low in dispositional fear show diminished reactivity to fearful expressions. For example, individuals high in psychopathy show reduced behavioral and brain response to emotional face stimuli, particularly fearful faces (cf. Blair, 2006). Notably, research on youth with conduct problems has demonstrated reduced behavioral (Blair, Colledge, Murray, & Mitchell, 2001) and amygdala (Marsh et al., 2008) reactivity to fear faces, specifically in children with callous–unemotional traits—akin to the emotional and interpersonal features of psychopathy in adulthood, which have been linked to deficits in fear-potentiated startle (cf. Patrick & Bernat, 2009b; see next major section below). However, it is important to note that amygdala damage does not invariably result in impaired recognition of fear faces, or impairments limited to processing of fearful expressions (Adolphs et al., 1999). Furthermore, as noted earlier, there is compelling evidence that the amygdala plays a role in the processing of positive as well as negative emotional events. Thus it remains to be determined whether impairments in facial affect processing in psychopathy reflect deficits in fear tied specifically to the amygdala, or broader impairments in emotional sensitivity extending beyond the amygdala.

Related to the use of visual stimuli such as fearful faces to index individual differences in reactivity of the core defensive system, a key issue to consider is the nature of the processing task used to assess brain reactivity differences. For example, standard picture-viewing tasks in which pictorial stimuli are presented individually for durations of several seconds are likely to elicit activation in diverse regions of the brain associated with processing at varying levels (e.g., emotional, attentional, memorial–imaginal, etc.). Tasks in which stimuli are presented fleetingly (e.g., Junghoefer, Bradley, Elbert, & Lang, 2001) or under conditions that preclude higher elaborative processing (e.g., Öhman & Soares, 1994) may be particularly useful for evaluating individual differences in affective sensitivity at the primary subcortical (amygdala) level. In this regard, an intriguing new methodology for investigating low-level affective processing is the interocular suppression paradigm, a variant of binocular rivalry in which stimuli are presented "invisibly" to one eye by presenting a more salient, imperative visual stimulus concurrently to the other eye. Using functional MRI, Jiang and He (2006) demonstrated that, in contrast with results from a normal (visible) viewing condition in which fearful faces were seen to activate the amygdala by way of the fusiform face area, under conditions of interocular suppression fearful faces activated the amygdala via the superior temporal sulcus—indicating that processing in this condition was limited to more primitive pathways. Jiang and colleagues (2009) have replicated and extended these findings, using event-related potential (ERP) measures. Although this technique has not been used to date in the study of individual differences in affect, it holds clear potential in this regard.

Other task procedures in which physiological measures have been used to index individual differences in defensive reactivity include aversive conditioning tasks (e.g., Flor, Birbaumer, Hermann, Ziegler, & Patrick, 2002), procedures involving anticipation of an impending stressor (cf. Hare, 1978), and dual-attention tasks in which fear cues are presented incidentally in conjunction with primary task cues (e.g., Curtin et al., 2001; Dvorak-Bertsch, Curtin, Rubinstein, & Newman, 2007). Existing tasks such as these provide further avenues for identifying physiological indicators of trait fear. It seems likely that some candidate physiological measures of defensive reactivity will ultimately prove more effective as indicators of general distress (reflecting hyperreactivity of the extended amygdala system) than of trait fear. For example, as noted above, there is evidence that enhanced sensitization of the startle response under conditions of prolonged stress or uncertainty operates as an index of general anxiety/distress. Other physiological indices that may emerge as indicators of general distress as opposed to trait fear include persistence of startle potentiation following the offset of a discrete

aversive stimulus (Jackson et al., 2003) and right frontal cerebral hemispheric asymmetry (Davidson, Pizzigalli, Nitschke, & Putnam, 2002; Heller & Nitschke, 1998).

Inhibitory Control

What brain systems/mechanisms underlie individual differences in the capacity to regulate affective and behavioral expression and to constrain impulses? Several lines of evidence point to anterior brain structures, including the prefrontal cortex (PFC) and anterior cingulate cortex (ACC), as playing crucial roles in this processing domain. With regard to the PFC, lesions of frontal brain regions are known to result in impulsive, externalizing behavior (Blumer & Benson, 1975; Damasio, Tranel, & Damasio, 1990), and individuals exhibiting or at risk for impulse control problems of various types show deficits on neuropsychological tests of frontal lobe function (Barkley, 1997; Morgan & Lilienfeld, 2000; Peterson & Pihl, 1990; Tarter, Alterman, & Edwards, 1985). The PFC is thought to be important for "top-down" processing—that is, the guidance of behavior by internal representations of goals or states. The PFC appears to be 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) have proposed that 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 strategies required 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.

In this regard, the PFC includes subdivisions that play differing roles in the guidance of behavior. The dorsolateral PFC, which has close connections with sensory association cortices and projects to varying premotor and motor areas in the medial and lateral frontal lobes, operates to encode relations between stimulus events and thereby represent rules (mappings) required to perform complex tasks. It is particularly important for active processes that involve top-down ("cognitive") control of behavioral responses (cf. Petrides, 2000). Ventromedial and orbitofrontal regions of the PFC (collectively termed the orbitomedial PFC; Blumer & Benson, 1975) connect more directly and extensively with medial temporal limbic structures (including the amygdala, hippocampus and associated neocortex, and hypothalamus) and appear to play a greater role in the anticipation of affective consequences of behavior (Bechara, Damasio, Tranel, & Damasio, 1997; Wagar & Thagard, 2004), in the unlearning of stimulus–reward associations (i.e., reversal learning) (Dias, Robbins, & Roberts, 1996; Rolls, 2000), and in the regulation of emotional reactivity and expression (Damasio et al., 1990; Davidson et al., 2000).

One brain response measure that has demonstrated reliable associations with differing forms of disinhibitory psychopathology is the P300 (or P3; see below)—a positive brain potential response, maximal over parietal scalp regions, that follows the occurrence of infrequent, attended targets in a stimulus sequence. It has long been known that individuals with (or at risk for) alcohol problems show reduced P300 response amplitude (e.g., Begleiter, Porjesz, Bihari, & Kissin, 1984; Porjesz, Begleiter, & Garozzo, 1980; for a review, see Polich, Pollock, & Bloom, 1994). More recent studies have shown reduced parietal P300 in relation to various other externalizing disorders, including drug dependence (e.g., Attou, Figiel, & Timsit-Berthier, 2001; Biggins, MacKay, Clark, & Fein, 1997), nicotine dependence (e.g., Anokhin et al., 2000), child conduct disorder (e.g., Bauer & Hesselbrock, 1999a, 1999b), and adult antisocial personality disorder (e.g., Bauer, O'Connor, & Hesselbrock, 1994). In addition, reduced P300 is known to be associated with risk for these other disorders, as well as with active symptoms (Brigham, Herning, & Moss, 1995; Iacono, Carlson, Malone, & McGue, 2002).

Patrick et al. (2006) tested the hypothesis that reduced P300 amplitude might reflect generalized externalizing vulnerability in a large sample of male twins (*N*

= 969). Higher scores on the externalizing factor estimated from symptoms of conduct disorder, adult antisocial behavior, alcohol dependence, drug dependence, and nicotine dependence were robustly associated with reduced amplitude of P300 response, and mediation analyses revealed that externalizing factor scores accounted for associations between individual diagnostic variables and reduced P300 amplitude. Furthermore, a principal-components analysis in which the diagnostic measures of externalizing were included along with P300 amplitude yielded a single dominant factor on which all indicators showed significant loadings. The fact that P300 loaded significantly (albeit modestly; see Figure 22.2) with the symptom variables on a common factor, rather than defining a separate method component, indicated that it was tapping the same underlying construct as the symptom variables. In a follow-up study that capitalized on the twin composition of this sample, Hicks and colleagues (2007) subsequently demonstrated that the relationship between externalizing factor scores and reduced P300 amplitude in this sample was attributable to overlapping genetic influences. These results indicate that reduced P300 directly reflects some alteration in brain function associated with the broad, strongly heritable vulnerability to disorders within the externalizing spectrum. Although for many years the P300 has been viewed as a distributed brain response reflecting activity in multiple brain regions, recent research on the neutral generators underlying this response points to an important role for prefrontal brain regions (see, e.g., Dien, Spencer, & Donchin, 2003; Nieuwenhuis, Aston-Jones, & Cohen, 2005).

Relevant to this, a follow-up study by our laboratory group has produced evidence of

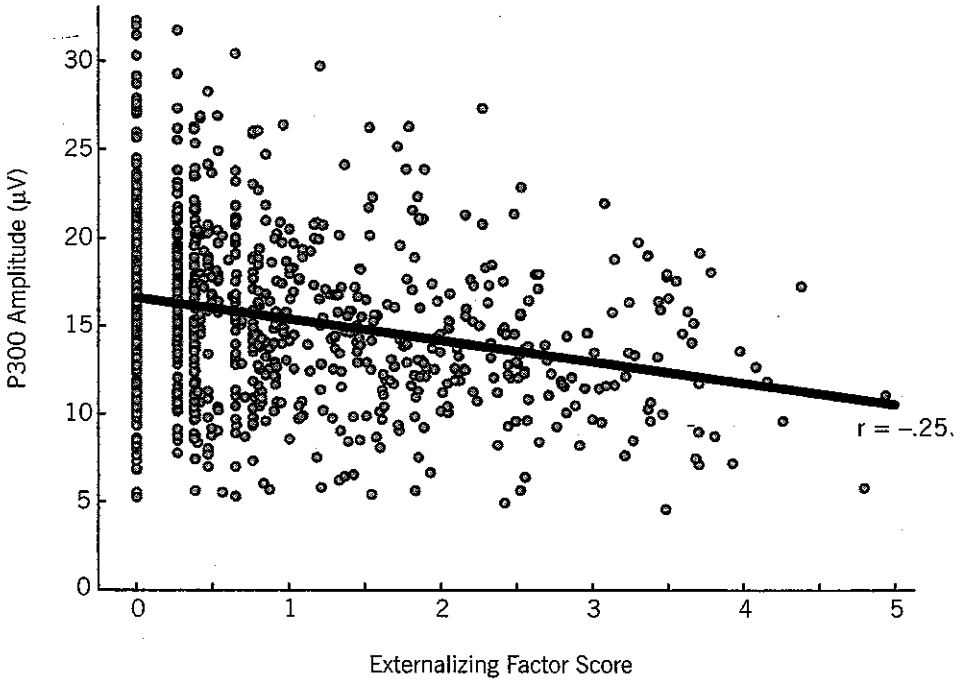

FIGURE 22.2. Scatterplot of the association, within a sample of male adolescents recruited from the community (N = 969), between mean amplitude of P300 response to task stimuli in a visual oddball procedure and continuous scores on the broad externalizing factor derived from a principal-components analysis of symptom scores for varying impulse control disorders. Solid line is best-fitting regression line. A standard geometric transformation was applied to the raw factor score data in order to vertically align low scores on externalizing; the data were normalized to unit-length axes prior to rotation and rescaled to the original units afterward. For purposes of plotting, the minimum score on the externalizing factor was subtracted from each resultant value, such that the 0 point on the x-axis represents the minimum score rather than the mean. From Patrick et al. (2006). Copyright 2006 by Blackwell Publishing. Reprinted by permission.

an augmented association between externalizing tendencies and diminished P300 at frontocentral versus parietal scalp sites, particularly for novel task stimuli that are known to preferentially activate anterior brain regions. Externalizing tendencies in this study were indexed by overall scores on an abbreviated (100-item) screening version of the ESI. The experimental task consisted of a three-stimulus visual oddball task (Bernat, Patrick, Cadwallader, van Mersbergen, & Seo, 2003). In addition to frequent nontarget (oval) and less frequent target (schematic "head") stimuli requiring a response, the task included infrequent novel stimuli, consisting of color picture stimuli. Target stimuli in a task of this sort elicit a P300 response that is maximal at parietal scalp sites. In contrast, novel stimuli evoke a P300 response—termed the "novelty P3" (Courchesne, Hillyard, & Galambos, 1975), to distinguish it from the target P300 (P3) response—that is maximal at frontocentral scalp sites. Available data indicate a prominent role of lateral PFC in the processing of novel stimuli (see Nieuwenhuis et al., 2005), and ERP source localization work points to a supporting role for the ACC in the generation of the novelty P3 response (Dien et al., 2003).

This study replicated our prior finding of reduced P3 amplitude to target stimuli as a function of higher externalizing tendencies—in this case, defined by scores on a carefully designed self-report inventory, the ESI, rather than by disorder symptoms as in the Patrick and colleagues (2006) study. In addition, we found a robust negative relationship between externalizing tendencies and P3 response to novel (picture) stimuli. The negative association between externalizing and P3 was stronger at anterior than at posterior scalp sites, particularly in the case of the novel picture stimuli. The enhanced magnitude of this effect at anterior sites is consistent with the hypothesis that the association between reduced P3 and externalizing reflects a deviation of some kind in frontal brain processing.

Another brain region important to regulating behavior is the ACC, which connects with premotor and supplementary motor regions as well as limbic structures (including the amygdala and hippocampus) and the PFC. The ACC has been conceptualized as a system that invokes the control functions of the PFC as needed to perform a task successfully, either by detecting errors in performance as they occur (Gehring, Coles, Meyers, & Donchin, 1995; Scheffers, Coles, Bernstein, Gehring, & Donchin, 1996), by monitoring conflict among 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). The ACC has also been implicated in affective–evaluative processing, with rostral–ventral areas thought to be more involved in the processing of emotional information, and dorsal areas more involved in the processing of cognitive information (Bush, Luu, & Posner, 2000). Impairments in ACC function would be expected to interfere with the ability to inhibit prepotent behavioral responses, to mediate between conflicting action tendencies, and to avoid repetition of errors.

In addition to studying reduced P300, we have undertaken investigations of the error-related negativity (ERN) as a physiological indicator of disinhibitory/externalizing tendencies. The ERN, a brain potential response that occurs following errors in performance, is believed to arise from the ACC (Dehaene, Posner, & Tucker, 1994; Holroyd, Dien, & Coles, 1998; Luu, Flaisch, & Tucker, 2000; Miltner, Braun, & Coles, 1997). Two variants of the ERN have been documented in the literature: (1) the response ERN (rERN), which occurs following errors in a speeded performance task in the absence of feedback; and (2) the feedback ERN (fERN), which occurs in response to feedback signaling an undesired (loss) outcome. The rERN been interpreted as the product of an endogenous (internal) action-monitoring process that relies upon ongoing maintenance of a task directive in order to register the occurrence of errors (Holroyd & Coles, 2002; Holroyd, Larsen, & Cohen, 2004; Mars et al., 2005). The fERN, on the other hand, has been interpreted as a direct response to an exogenous (external) error cue. Recent published work by our group (Hall et al., 2007) has demonstrated significantly reduced rERN response following performance errors in a flanker task in individuals high in externalizing tendencies as indexed by the ESI-100. This finding coincides with other published work demonstrating reduced rERN in relation to

disinhibitory personality traits (Dikman & Allen, 2000; Pailing & Segalowitz, 2004) and states (Ridderinkhoff et al., 2002).

However, in a recent follow-up study (Bernat, Nelson, Steele, Patrick, & Gehring, 2010), we found no evidence of reduced fERN in high-externalizing individuals following *externally presented* loss feedback in a simulated gambling task. A technical challenge in this study was that the negative-going fERN response reflecting the motivational impact of the *loss* component of feedback overlapped in time with a positive-going P300 component reflecting elaborative postevent processing of feedback stimuli per se (i.e., beyond initial encoding of its gain–loss significance). As a consequence of this overlap, individuals high in externalizing appeared, if anything, to show *enhanced* negativity of response during the time window of the fERN—an effect clearly opposite to our prediction. To clarify this result, we employed a method called "time–frequency analysis" (Bernat, Williams, & Gehring, 2005)—a technique for separating distinct but overlapping ERP components by considering differences in underlying oscillatory (frequency) characteristics of one versus another—to isolate two distinct components underlying the ERP response to feedback stimuli: (1) a higher-frequency (theta band) component reflecting the fERN response to loss stimuli in particular, and (2) a lower-frequency (delta band) component reflecting the generic P300 response to gain as well as loss feedback stimuli. We found that high-externalizing individuals showed normal theta fERN activity following loss feedback, while showing significantly reduced P300 response to feedback stimuli in general (i.e., whether indicative of gain or loss). This pattern of results has two important implications. First, it indicates that reduced rERN response in high-externalizing individuals does not reflect a deficit in ACC function per se, but rather processing impairments in other brain regions crucial for endogenous action monitoring (e.g., regions of PFC) but not for registration of external performance feedback. Second, it indicates that deficits in inhibitory control associated with disorders of this type entail impairments in associative–elaborative processing of events (e.g., comparing and integrating transient cognitive–affective representations with representations stored in long-term memory; cf. Ericsson & Kinsch, 1995), rather than impairments in primary affective processing.

In summary, evidence to date points to dysfunctions in anterior brain circuitry, including the PFC and affiliated brain regions with which it interacts (such as the ACC), as a substrate for deficient inhibitory control. The consequence of an underlying weakness in this circuitry would be 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 (cf. Miller & Cohen, 2001). As described by Patterson and Newman (1993), a weakness of this sort would impair an individual's ability to shift from an ongoing response set to a reflective orientation in the face of conflict, resulting in a failure to modify subsequent actions on the basis of undesirable outcomes. Furthermore, dysfunction in the PFC–ACC systems would compromise an individual's ability to (1) ascribe motivational significance to representations for more complex and distal, but ultimately more fulfilling, behavioral goals; (2) anticipate obstacles and formulate strategies for overcoming them before they become overwhelming (e.g., deal proactively with frustrating or threatening circumstances); (3) detect conflict between competing response tendencies (i.e., evaluate, online, the probability of making an error); and (4) monitor and regulate affective responses in the service of distal goals. As an example of this, Davidson and colleagues (2000) proposed that persistent impulsive–aggressive behavior arises from dysfunctions in PFC–ACC circuitry that lead to impairments in online conflict detection and down-regulation of negative affect.

Role of Defensive Reactivity and Inhibitory Control in Psychological Disorders

Internalizing Disorders

Fearfulness has both adaptive and maladaptive aspects. Defensive activation in the presence of threat cues is biologically adaptive, and thus normative. However, fear that is disproportionately intense or persistent in relation to evoking circumstances is consid-

ered pathological. As noted earlier, internalizing disorders appear to fall into two distinct subgroups: fear disorders and distress (anxious misery) disorders (Krueger, 1999b; Watson, 2005). Fear disorders are characterized by physiological hyperreactivity, either in relation to external eliciting stimuli (in the case of specific and social phobia) or internal physiological cues (in the case of panic disorder), whereas distress disorders are marked by prominent anxiety and dysphoria not tied to specific eliciting cues. Individuals who exclusively manifest fear disorders tend to be better adjusted psychologically and show less impairment in areas of life unrelated to their fears than individuals exhibiting distress disorders (Cook, Melamed, Cuthbert, McNeil, & Lang, 1988; Cuthbert et al., 2003). The implication is that fear disorders in themselves are less pathological conditions, reflecting extreme variants of normative fearfulness, in comparison with distress disorders.

What factors give rise to the more pathological, dysregulated NA characteristic of distress disorders? Rosen and Schulkin (1998) have theorized that the pathological anxiety observed in disorders like PTSD reflects hyperexcitability of brain systems that underlie fear expression, particularly the amygdala and extended amygdala. According to Rosen and Schulkin (1998), constitutional differences in the threshold for activation of these underlying brain systems, in conjunction with adverse experiences that activate them repeatedly or for protracted periods, lead to sensitization of these systems—manifested psychologically as intense and persistent negative mood, hypervigilance, and a sense of uncontrollability (i.e., the defining elements of distress disorders). Consistent with this model, we hypothesize that high dispositional defensive reactivity—defined in neurobiological terms as constitutionally high reactivity of the amygdaloid fear system—represents one crucial vulnerability factor for the development of internalizing disorders. As noted earlier, there is evidence that individual differences in reactivity of this system have a genetic contribution (e.g., Harari et al., 2002) and are evident behaviorally from a very early age (Goldsmith & Campos, 1982; Kagan, 1994). Reciprocally, there is evidence that individuals high in core personality features of psychopathy, who (as noted earlier) exhibit impairments in fear reactivity as indexed by startle potentiation, and who demonstrate reduced amygdala reactivity to fearful face stimuli (Blair, 2006; Marsh et al., 2008), show relative immunity to internalizing symptoms and syndromes (Blonigen et al., 2005; Hicks & Patrick, 2006).

Because the psychometric operationalization of defensive reactivity as trait fear focuses on scales that index the emotional experience of fear (or lack of it) in relation to events and situations, this construct is likely to have relevance to fear disorders—in particular, specific and social phobias, which by definition entail fear that is tied to specific stimuli and situations. However, if dispositional hyperreactivity of the core defensive motivational system contributes to pathological anxiety syndromes as postulated by Rosen and Schulkin (1998), high trait fear should also exhibit some association with internalizing disorders in the "distress" subcategory. Relevant to this, Table 22.1 presents data from a mixed-gender sample of adults from the community (N = 187) who were assessed for trait fear with an abbreviated 55-item screening inventory (TF-55) consisting of selected items from the various fear and fearlessness inventories examined by Kramer and colleagues (2010) that provided highly effective estimation (cross-validated multiple R = .94) of scores on the general fear–fearlessness factor emerging from their structural analysis.[2] Participants in this sample were also administered the Inventory of Depression and Anxiety Symptoms (IDAS; Watson et al., 2007), a self-report inventory designed to assess for symptoms of depression and affiliated anxiety disorders. The inventory includes (1) a broad scale assessing dysphoria (i.e., the overarching mood component of depression, indexed separately from its accompanying symptoms); (2) subscales assessing specific domains of depressive symptoms; (3) a broad scale indexing overall depressive symptoms (composed of selected items from the broad dysphoria scale and narrower depressive symptom scales); and (4) subscales assessing symptoms of anxiety disorders that commonly co-occur with depression (i.e., social phobia, panic disorder, PTSD).

Consistent with expectation, trait fear scores were correlated most robustly with

TABLE 22.1. Correlations of Trait Fear Scores with Broad Dysphoria/Depression Scales and Specific Symptom Subscales of the Inventory of Depression and Anxiety Symptoms (IDAS; Watson et al., 2007)

IDAS scale/subscale score	r	$r_{[/\text{Social Anxiety}]}$	$r_{[/\text{Dysphoria}]}$
Broad Dysphoria scale	.36**	.10	—
Broad Depression scale	.35**	.12	.05
Depression symptom subscales			
Lassitude	.26**	.03	.01
Insomnia	.14	−.01	−.10
Suicidality	.18*	.05	.10
Appetite Loss	.05	−.11	−.17
Appetite Gain	.21*	.06	.06
Ill Temper	.26**	.08	.05
Well-Being	−.31**	−.25*	−.24*
Anxiety symptom subscales			
Social Anxiety	.49**	—	.37**
Panic	.13	−.08	−.09
Traumatic Intrusions	.18*	.00	−.04

Note. Sample consisted of 187 adult men and women recruited from the community. Trait fear scores are total scores on a 55-item inventory composed of items from various established self-report measures of fear and fearlessness (for details, see Kramer et al., 2010). $r_{[/\text{Dysphoria}]}$, partial correlation between trait fear and IDAS scale/subscale after controlling for scores on the IDAS Dysphoria scale. $r_{[/\text{Social Anxiety}]}$, partial correlation between trait fear and IDAS scale/subscale after controlling for scores on the IDAS Social Anxiety scale.
*$p < .05$. **$p < .001$.

symptoms of social anxiety (i.e., social phobia; Table 22.1, leftmost r column). However, trait fear scores also evidenced reliable associations with dysphoric mood and overall depressive symptoms, as well as with some specific symptoms of depression—most notably lassitude (fatigability), ill temper (irritability), and low well-being. Trait fear also showed a reliable association with proneness to intrusive thoughts/images characteristic of PTSD but only a marginal relationship ($p = .07$) with discrete bodily symptoms characteristic of panic disorder. Furthermore, partial correlations depicted in the middle r column of Table 22.1 indicate that bivariate correlations of trait fear with broad dysphoria/depression and most affiliated symptoms of depression were accounted for by anxiety experienced in relation to social events/situations (i.e., social anxiety symptoms); in contrast, the association between trait fear and social anxiety symptoms remained highly significant after controlling for depressed mood (dysphoria; see Table 22.1, rightmost r column). These results are consistent with the idea that high dispositional fear is central to phobic disorders in particular, but that it also plays some role in distress-related syndromes.

A crucial question that remains to be answered is what factors lead some highly fearful individuals to develop disorders marked by generalized distress (i.e., chronic anxiety and dysphoria), whereas others develop only focal phobias. The answer, we believe, lies in other dispositional variables and pathogenic environmental influences that interact with high trait fear (hyperreactivity of the amygdala to aversive events) to promote sensitization of not only the core fear system but also its affiliated "anxiety system" (i.e., the extended amygdala/BNST). For example, dispositional factors that enable an individual to counteract or constrain defensive reactions to discrete environmental stressors, and thereby to limit the intensity and duration of fear episodes, would operate against general sensitization. On the other

hand, exposure to highly intense, repeated, unpredictable stress (e.g., such as that experienced by combat veterans or victims of chronic abuse) would operate to enhance sensitization (cf. Rosen & Schulkin, 1998). The availability of direct neurophysiological assessment of dispositional fear would provide a basis for prospective longitudinal studies of how vulnerability in the form of enhanced responsiveness of the core (amygdala) defensive system gives rise to distress or fear disorders of differing kinds as a function of other intersecting constitutional and environmental factors.

Externalizing Disorders

The conceptual model proposed here conceives of weak inhibitory control—defined in neurobiological terms as deviations in the functioning of anterior brain circuits that operate to modulate affect and behavior on the basis of distal (nonimmediate) goals/consequences (Davidson et al., 2000; Patrick & Bernat, 2009a; Patterson & Newman, 1993)—as an underlying vulnerability or diathesis for impulse control (externalizing) problems of various kinds. The fact that this general vulnerability is predominantly heritable (Kendler et al., 2003; Krueger et al., 2002; Young et al., 2000) and accounts for substantial variance in diverse disorders makes it a crucial target for neurobiological research on problems of this kind. Recent research operationalizing a hierarchical model of impulse control problems and affiliated traits in the form of a quantitatively sophisticated psychometric instrument, the ESI (Krueger, Markon, et al., 2007), provides the foundation for systematic investigations of neurobiological processes related to this general vulnerability factor.

As described earlier, we have conducted recent investigations of processing deviations associated with high levels of general externalizing tendencies indexed by overall scores on an abbreviated (100-item) screening version of the ESI. Overall scores on the ESI-100 correlate very highly ($r > .95$) with scores on the full 415-item ESI.[3] In an initial published study of this type involving undergraduate participants ($N = 92$; Hall et al., 2007), we reported correlations between scores on the ESI-100 and criterion variables consisting of well-established self-report measures of antisocial deviance (Behavior Report on Rule-Breaking; Nye & Short, 1957), alcohol dependence (Alcohol Dependence Scale; Skinner & Allen, 1982), drug abuse (Short Drug Abuse Screening Test; Skinner, 1982), and adherence to societal norms (Socialization Scale; Gough, 1960). These correlations are shown in Table 22.2. Table 22.2 also presents, for a different sample consisting of 144 incarcerated male offenders, correlations between scores on the ESI-100 and symptoms of varying DSM-IV-TR impulse control disorders assessed via clinical interview. Uniformly robust correlations are evident between generalized externalizing tendencies as indexed by the ESI-100 on the one hand, and relevant self-report and interview-based criterion measures on the other.

TABLE 22.2. Correlations of Externalizing Scores with (1) Criterion Variables Assessed via Self-Report and (2) Symptoms of Differing DSM-IV-TR Impulse Control Disorders Assessed via Clinical Interview

Measure	*r*
Self-report criterion variables[a]	
Behavior Report on Rule-Breaking	
Overall behaviors	.83**
Adult behaviors	.75**
Adolescent behaviors	.76**
Alcohol Dependence Scale	.64**
Short Drug Abuse Screening Test	.61**
Socialization Scale	−.61**
DSM-IV-TR disorder symptoms[b]	
Antisocial personality	
Overall symptoms	.54**
Child symptoms	.42**
Adult symptoms	.60**
Alcohol dependence	.30**
Nicotine dependence	.60**
Other drug dependence	.34**

Note. Externalizing scores are overall scores on a 100-item version of the Externalizing Spectrum Inventory (ESI; Krueger, Markon, et al., 2007).

[a]Sample for self-report criterion variables consisted of 92 male and female university students recruited from undergraduate classes (cf. Hall et al., 2007).

[b]Sample for DSM-IV-TR symptom variables consisted of 144 adult male offenders recruited from a state correctional facility.

**$p < .001$.

Personality Disorders

Prominent researchers in the personality disorders area (e.g., Clark, Livesley, Schroeder, & Irish, 1996; Krueger, Skodol, Livesley, Shrout, & Huang, 2007; Morey, Gunderson, Quigley, & Lyons, 2000; Widiger & Sanderson, 1995) have presented evidence that symptoms of these disorders can be organized along broad thematic lines paralleling major dimensions of personality. Researchers in this area have also postulated that common neurobiological mechanisms, with ties to broad personality and temperament constructs, contribute to the emergence of personality disorders of differing types (e.g., Siever, 2000; Siever & Davis, 1991).

Furthermore, it is well established that personality syndromes coded on Axis II of DSM co-occur systematically with major clinical disorders coded on Axis I. In this regard, clinical and epidemiological studies (cf. Zuckerman, 1999) have revealed high comorbidity of Cluster C personality disorders with Axis I internalizing (fear and distress) disorders in particular, and of Cluster B personality disorders with Axis I impulse control disorders (e.g., adult alcohol and drug dependence; childhood ADHD, oppositional defiant disorder, and conduct disorder; and adult antisocial personality disorder) as well as some Axis I internalizing disorders (those within the distress subgroup especially). Related to this, various writers (e.g., Krueger, 1999b; Tellegen, 1985; Tellegen & Waller, 2008; Trull, 1992; Trull & Sher, 1994) have presented evidence that broad trait-dispositional constructs show empirical relations with personality syndromes coded on Axis II of DSM, as well as with major clinical disorders coded on Axis I. These and other findings have led to calls for an integration of Axis I and Axis II disorders in terms of broad dimensional constructs (e.g., Krueger, 2005; Livesley, Schroeder, Jackson, & Jang, 1994).

The neurobehavioral constructs of defensive reactivity and inhibitory control emphasized in this chapter have clear conceptual relevance to varying personality disorders coded on Axis II of DSM. The construct of defensive reactivity appears relevant in particular to personality disorders represented in Cluster C, which are characterized by fearfulness and anxiety (American Psychiatric Association, 2000). The construct of weak inhibitory control in turn has particular relevance to disorders in Cluster B, which are marked by behavioral impulsiveness and dysregulated emotion. Findings shown in Table 22.3, based on data from a mixed-gender sample of adults recruited from the community (N = 190), provide empirical confirmation of these linkages. Participants in this sample were assessed for trait fear and externalizing tendencies with the abbreviated screening measures of these constructs described earlier (TF-55, ESI-100); in addition, they were assessed for symptoms of DSM-IV Cluster B and C personality disorders with the Screening Questionnaire of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II; First, Spitzer, Gibbon, & Williams, 1997). Consistent with expectation, trait fear scores show robust positive correlations with all personality disorders in Cluster C (with the magnitude particularly strong for avoidant personality disorder), whereas externalizing scores show robust positive associations with all personality disorders in Cluster B (in this case, all similar in magnitude). In addition, trait fear shows a robust *positive* association specifically with borderline personality disorder in Cluster B,[4] and significant *negative* correlations with both histrionic and antisocial personality disorders. As a function of these relations, and as a function of the statistical independence between trait fear scores and externalizing scores (e.g., in this sample, $r = -.069$, $p > .34$), trait fear scores contributed to improved prediction of each of these Cluster B disorders when entered concurrently with externalizing scores in a regression model. In contrast, externalizing scores showed no association with any of the personality disorders in Cluster C. These results provide evidence of systematic relations between psychometric measures of these neurobehavioral constructs and DSM personality disorder syndromes, and they encourage the idea that trait variations in defensive reactivity and inhibitory control represent key neurobiological substrates for personality disorders of differing types.

Criminal Psychopathy

In his classic volume *The Mask of Sanity* (1976), Cleckley characterized psychopathy

TABLE 22.3. Predictive Associations for Trait Fear Scores and Externalizing Scores with Symptoms of DSM-IV-TR Cluster B and C Personality Disorders Assessed via the SCID-II Screening Questionnaire

Symptom score	Trait fear		Externalizing		
	r	*β*	*r*	*β*	*R*
Cluster B personality disorders					
Histrionic	−.18*	−.16*	.28**	.27**	.32**
Narcissistic	.07	.09	.26**	.26**	.27**
Borderline	.30**	.32**	.25**	.27**	.40**
Antisocial (child symptoms)	−.24*	−.22*	.32**	.31**	.39**
Cluster C personality disorders					
Avoidant	.70**	.70**	.07	.12	.71**
Dependent	.31**	.32**	−.02	.00	.32**
Obsessive–compulsive	.30**	.31**	.09	.11	.32**

Note. Sample consisted of 190 adult men and women recruited from the community. Trait fear scores are total scores on a 55-item inventory composed of items from various established self-report measures of fear and fearlessness (for details, see Kramer et al., 2010). Externalizing scores are overall scores on a 100-item version of the ESI (Krueger, Markon, et al., 2007). *r*, zero-order correlation of personality disorder variable with trait fear or externalizing scores. *β*, beta coefficient for prediction of personality variable by trait fear or externalizing when scores on both were included together in a regression model. *R*, multiple-regression coefficient for prediction of personality variable by trait fear and externalizing when scores on both were included together in a regression model. For antisocial personality under Cluster B personality disorders, data were available for child symptoms only because questions pertaining to the adult symptoms are not included in the SCID-II Screening Questionnaire.
*$p < .05$. **$p < .001$.

as a dualistic syndrome. On one hand, psychopathic individuals present as personable, carefree, and emotionally resilient. On the other, they exhibit severe behavioral problems that bring them into repeated conflict with society. The dominant assessment instrument in contemporary psychopathy research, Hare's (1991, 2003) Psychopathy Checklist—Revised (PCL-R), was developed to identify individuals fitting Cleckley's clinical description within correctional or forensic settings. Although the PCL-R was developed to measure psychopathy as a unitary construct, structural analyses have shown that it contains distinctive subgroups of items (factors) that, while correlated, nonetheless show diverging relations with external criterion variables. Most published research has focused on the original two-factor model (Hare et al., 1990; Harpur, Hakstian, & Hare, 1988), in which PCL-R factor 1 comprises the interpersonal and affective features of psychopathy and factor 2 encompasses the antisocial deviance features. Higher factor 1 scores are associated with higher narcissism and Machiavellianism (Hare, 1991; Harpur, Hare, & Hakstian, 1989) and lower empathy (Hare, 2003). Factor 1—in particular, its variance that is separate from factor 2—shows positive relations with measures of social dominance (Harpur et al., 1989; Verona, Patrick, & Joiner, 2001), and in some studies with achievement (Verona et al., 2001) and trait positive affect (Patrick, 1994). Thus scores on PCL-R factor 1 evidence positive relations with some adaptive personality traits (interpersonal dominance and, in some work, tendencies toward achievement and trait positive affect; cf. Patrick, 2007). In contrast, PCL-R factor 2 shows associations mainly with indicators of deviancy, including aggression, impulsivity, and general sensation seeking; child and adult symptoms of DSM antisocial personality disorder; criminal history variables, such as onset and frequency of offending; and alcohol and drug dependence.

A two-process theory of psychopathy has been formulated to account for the distinctive components of psychopathy evident in the PCL-R (Fowles & Dindo, 2006; Patrick & Bernat, 2009b; Patrick & Lang, 1999).

This model focuses on the neurobehavioral constructs of defensive reactivity and inhibitory control emphasized here. The affective–interpersonal features of psychopathy associated with PCL-R factor 1 are theorized to reflect in part a lack of normal defensive reactivity, whereas the behavioral deviance features associated with factor 2 are theorized to reflect impairments in inhibitory control systems. Consistent with this, as noted earlier, individuals high in affective–interpersonal features of psychopathy show reduced potentiation of the startle reflex during aversive cuing (e.g., Patrick, 1994; Patrick, Bradley, & Lang, 1993) and reduced amygdala responsiveness to fearful face stimuli (Blair, 2006; Marsh et al., 2008). With regard to factor 2, scores on this component of the PCL-R show a close association with the broad externalizing factor of psychopathology (Patrick, Hicks, Krueger, & Lang, 2005) and selectively predict enhanced errors of commission in a well-established conflict task (Molto, Poy, Segarra, Pastor, & Montanes, 2007) as well as reductions in oddball P300 response (Venables, Reich, Bernat, Hall, & Patrick, 2008). From the perspective of this model, a clearer understanding of etiological mechanisms underlying psychopathy can be gained by directly assessing individuals on psychometric dimensions of trait fear and externalizing, and by using physiological measures to investigate deviations in cognitive and affective processing associated with varying positions along these dimensions (Patrick & Bernat, 2009b). Research of this kind can both draw on and inform parallel work focusing on the roles of trait fear and externalizing and their neurobiological counterparts (defensive reactivity, inhibitory control) in disorders of anxiety/mood, impulse control, and pathological personality as defined within DSM.

Toward a Psychoneurometrics of Psychopathology: An Illustration

Although evidence discussed to this point indicates that psychometric measures of dispositional defensive reactivity (i.e., trait fear) and inhibitory control (i.e., externalizing tendencies) can help to bridge psychopathological phenotypes with neurobiological measures, our aim in this chapter is not to suggest that these psychometric variables should *replace* traditional diagnostic entities as referents for neurobiological studies of psychopathology. Rather, our aim is to encourage—alongside continuing neuroscientific studies of established diagnostic syndromes—systematic investigation of the neurophysiological correlates of these psychometric phenotypes as a step toward the development of direct *brain-based* measures of neurobehavioral trait constructs. This can be accomplished by routinely including precise psychometric measures of these target constructs in brain measurement studies involving moderate to large *N*'s, in order to identify reliable neurophysiological correlates of these constructs. Once multiple physiological indicators of these constructs have been identified, studies incorporating multiple known indicators (in the context of common as well as varying task procedures) can be conducted in order to map convergences and divergences among indicators.

To provide a concrete illustration of this approach, we have undertaken analyses of relations among differing brain potential response indicators of externalizing across differing tasks. Because participant samples for the three-stimulus oddball, rERN, and fERN studies described earlier (see the section, "Neurobiological Bases and Physiological Correlates") overlapped, we could directly compare brain response measures across these tasks for the 92 participants who completed all three. As mentioned, fERN theta response to explicit feedback stimuli was unrelated to ESI-100 externalizing scores, but the delta P3 response to these same feedback stimuli was reduced as a function of higher externalizing tendencies ($r = -.25$). Notably, delta P3 response in the feedback task showed a significant positive association with P3 reactivity to novel picture stimuli in the oddball task ($r = .30$), which (as mentioned earlier) was also reduced as a function of externalizing ($r = -.29$). Furthermore, both of these P3 response measures showed positive correlations with magnitude of rERN response in the flanker task (i.e., greater P3 predicted greater rERN; r's = .31 and .37 for feedback P3 and novelty P3, respectively).

Thus these three brain response indicators, each of which showed a significant negative association with ESI-100 externalizing scores, correlated significantly with one another. The implication is that these differing brain response measures tap *some process in common* that is related to externalizing tendencies. Notably, externalizing-related reductions in all three of these response measures were maximal at anterior (frontocentral) scalp sites. Taken together with the finding of *intact* fERN responding, these data encourage the idea that reduced rERN responding in high-externalizing individuals reflects impairment in anterior brain regions that participate with the ACC in the process of endogenous action monitoring. As noted earlier, we hypothesize that the PFC (more specifically, the dorsolateral PFC) is one such region.

As a further analysis, we entered these three brain response measures into a principal-components analysis along with ESI-100 externalizing scores. The analysis yielded evidence of a single dominant component, accounting for close to 50% of the overall variance in these four measures. To quantify their varying levels of effectiveness as indicators of a common factor, we performed a principal-axis factor analysis of scores on these four measures, solving for a single factor (per the results of the initial analysis). The loading of ESI-100 scores on this common factor ($r = -.49$), reflecting the shared variance among indicators, was comparable to the loadings for the three brain response measures (for feedback P3, novelty P3, and rERN, r's = .50, .54, and .66, respectively). Notably, the common factor emerging from this analysis represents a predominantly *neurophysiological* (ERP-based) externalizing factor on which the self-report ESI-100 measure also loaded. This result has important implications. It indicates that variations in inhibitory control can be assessed in terms of a composite *physiological* dimension. Given evidence for the high heritability of general externalizing tendencies (e.g., Krueger et al., 2002), together with data indicating that associations of externalizing with brain response measures such as P3 are mediated by common genetic influences (e.g., Hicks et al., 2007), this finding points to the possibility that scores on a *physiologically defined* dimension of inhibitory control could be used in future research as a basis for selecting at-risk individuals for neuroimaging and genetic studies of impulse control disorders.

The process of identifying reliable physiological indicators of neurobehavioral constructs such as defensive reactivity and inhibitory control, for which reliable psychometric referents already exist, is a process in which multiple investigators can participate. As described in the foregoing illustration, differing brain response indicators of externalizing tendencies as indexed by the ESI have already been identified, including rERN amplitude and varying manifestations of P3 response across differing tasks. Our efforts to operationalize a coherent psychometric dimension of trait fear are more recent, and startle reflex potentiation is the one variable to date that we have directly evaluated as an indicator of this dimension. However, as noted above (see the section, "Neurobiological Bases and Physiological Correlates"), the available literature points to various other candidate physiological indicators of trait fear. Furthermore, as discussed in the final section below, the psychoneurometric approach can potentially be applied to other dimensional psychometric phenotypes of relevance to psychopathology—including the broad distress and narrower positive affect and anhedonia factors associated with disorders in the internalizing spectrum (cf. Watson, 2005), and the callous aggression and addiction proneness subfactors that link particular subsets of problems/traits within the externalizing spectrum (Krueger, Markon, et al., 2007).

Figure 22.3 provides a schematic illustration of the psychoneurometric approach. As depicted in the figure, the approach entails (1) systematic efforts to identify *reliable physiological correlates* of a relevant behavioral phenotype within one or more psychologically meaningful task contexts, followed by (2) efforts to evaluate the *structure* of these physiological indicators (particularly the variance in each that intersects with the behavioral phenotype of interest; cf. Iacono, 1991)—both with the aims of refining physiological measurement of the neurobehavioral construct of interest, and clarifying the psychological meaning of physiological indicators derived from differing tasks. These

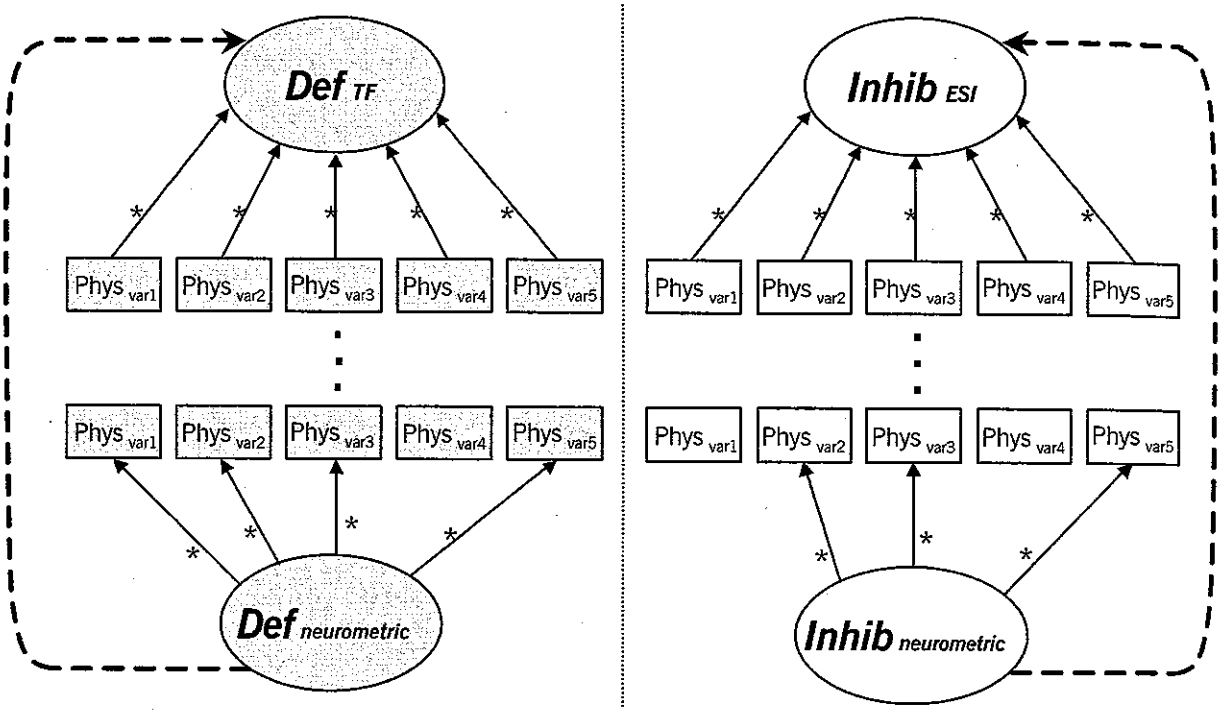

FIGURE 22.3. Schematic depiction of the psychoneurometric approach as applied to target constructs of defensive reactivity (*Def*) and inhibitory control (*Inhib*). The first stage of the approach involves identifying reliable physiological indicators ($Phys_{var1}$, $Phys_{var2}$, etc.) of these constructs operationalized *psychometrically*, as trait fear (Def_{TF}) and externalizing ($Inhib_{ESI}$). This is followed by mapping of interrelations among physiological indicators of each construct, in order to (1) establish statistically reliable *neurometric* measures of defensive reactivity ($Def_{neurometric}$) and inhibitory control ($Inhib_{neurometric}$), and (2) gain understanding of brain circuits/processes that underlie individual differences in defensive reactivity and inhibitory control. Information gained regarding the convergence of differing physiological indicators derived from designated behavioral tasks, and the brain mechanisms underlying this convergence, feeds back into psychometric conceptualization/measurement of these target constructs (large, curved, dashed arrows on left and right sides of figure). This process continues iteratively until a coherent set of neurometric tasks/measures exists for assessing each target construct precisely and reliably.

steps are followed by efforts to (3) update conceptualization of the target neurobehavioral construct to accommodate insights gained from the structural analysis of physiological indicators (while retaining linkages to psychopathology); (4) revise behavioral operationalization of the target construct to incorporate the revised conceptualization; and (5) implement new or modified task protocols designed to increase convergence between revised behavioral phenotypes and physiological response measures within those tasks. This process continues iteratively to the point where a coherent array of physiological tasks/measures exists for operationalizing the targeted neurobehavioral construct in a precise and reliable manner.

Conclusions and Future Directions

Research aimed at elucidating the neurobiological underpinnings of psychopathology has been identified as a high priority by authorities in the mental health field. However, there is growing recognition that new investigative approaches are needed to establish bridges between traditional conceptualizations of psychopathology and variations in brain circuitry and function that relate to individual differences in behavior (Hyman, 2007). As a method for elucidating neurobiological mechanisms in psychopathology, the psychoneurometric approach described here has a number of notable features. First, it confronts the issue of diagnostic comor-

bidity among mental disorders by focusing on broad dispositional factors that differing disorders share, while acknowledging the role of unique etiological contributors to specific disorders. Second, it addresses the gap between diagnostic phenotypes (clinical disorders) and neurobiological systems by focusing on neurobehavioral trait constructs with demonstrable relevance to psychopathology. Third, it provides a means by which high-level quantitative/statistical methods developed to quantify constructs in the domains of personality and performance can be applied to the development of reliable neurophysiological measures of trait constructs relevant to psychopathology. Fourth, it provides an interface through which behavioral conceptualizations can directly guide efforts to identify psychopathology-relevant neurobiological processes/circuits—and, reciprocally, through which knowledge gained about relevant neurobiological processes/circuits can feed back into behavioral conceptualizations of psychopathology.

There are some important practical challenges to implementing an approach of this kind at levels required to ensure significant sustained progress. Psychometric development efforts require large participant samples and repeated rounds of data collection in order to establish the measurement properties of items/subtests. Relative to self-report and performance-based assessments, neurophysiological assessment procedures are generally more costly, time-consuming, and resource-intensive. Neuroimaging methods in particular pose challenges in terms of availability and expense. We believe that these challenges can be surmounted through coordinated efforts of multiple investigators employing less costly electrocortical (EEG/ERP) and peripheral physiological measures in larger-scale mapping and refinement efforts. In turn, work of this kind can inform and draw upon smaller-scale investigative efforts using costlier methods such as hemodynamic neuroimaging to extend understanding of brain circuits of emerging interest. The first step in pursuing a psychoneurometric approach to the study of psychopathology consists of studies with moderate to large samples aimed at identifying reliable neurobiological correlates of constructs such as trait fear and externalizing. As noted, this is an effort in which multiple investigators can participate either independently or in collaboration with one another—and, in the case of defensive reactivity and inhibitory control constructs, a variety of candidate indicators can be identified on the basis of existing published literature.

Regarding physiological measurement, we encourage the use of EEG/ERP as a methodology in moderate- to large-*N* studies exploring candidate indicators and evaluating their convergence. Among other advantages, EEG/ERP measures (1) directly reflect neural activity and thus can be interpreted in relation to models of brain structure and function; (2) are informative about cognitive/attentional as well as affective/motivational processes (e.g., Lang et al., 1997); and (3) yield precise information regarding temporal (time) and spectral (frequency) characteristics of brain activity, along with spatial (scalp site) information that can be used to estimate underlying neural sources of activity (cf. Patrick & Bernat, 2009a). With regard to localization of neural activity origins, the precision with which underlying neural sources can be estimated from surface EEG activity can be enhanced by recording from multiple scalp sites and referencing the activity to brain images acquired via MRI (e.g., Ding et al., 2007).

A further point is that the current chapter is necessarily limited in scope. Given constraints of space, we have focused largely on disorders in the mood/anxiety and impulse control domains (along with affiliated personality syndromes) because these represent some of the most commonly occurring disorders in the population. Furthermore, we have focused primarily on constructs of defensive reactivity and inhibitory control because these represent examples of trait constructs with clear neurobiological referents, and because available data point to a role for these constructs in multiple internalizing and externalizing disorders. However, the basic investigative strategy we have outlined is applicable to disorders of other sorts—including developmental disorders, appetitive (e.g., eating, sexual) disorders, and psychotic syndromes. Regarding target constructs for study, it seems likely that deviations in defensive reactivity and inhibitory control contribute to the symptomatic expression of at least some of these other disorders (see, e.g., Meehl, 1990). In addi-

tion, other neurobehavioral constructs in the domains of motivation, attention/cognition, and perception will need to be considered in relation to disorders of these other types.

As a final note, it bears emphasis that the methodological approach described here is intended as a supplement to, rather than as a substitute for—existing research strategies. In particular, we view the psychoneurometric approach as a paradigm for linking psychopathological conditions to neurobiological systems, not as a prescription for a particular program of research. Besides contributing to our understanding of brain substrates of psychopathology, we believe that this approach offers a path toward the development of reliable neurophysiological composite measures of trait constructs relevant to psychopathology. Neurophysiological trait measures of this type are likely to prove especially effective as selection criteria for neuroimaging and genetic studies of individuals at biological risk for psychopathology.

Note

1. When fearfulness is operationalized in terms of preference for safe but unstimulating activities over risky activities (e.g., as in the SSS-TAS subscale or the MPQ Harm Avoidance scale), fear scores tend to be uncorrelated with scores on trait anxiety measures (Tellegen & Waller, 2008). In contrast, when fearfulness is defined in terms of degree of negative emotion experienced in relation to unfamiliar or threatening objects or situations (as in the EAS-Fear, the FSS, and the TPQ-HA scale), fear scores tend to be moderately correlated with levels of trait anxiousness (Buss & Plomin, 1984).
2. A list of the TF-55 items can be obtained from us upon request.
3. Copies of both the full and abbreviated versions of the ESI can be obtained from us upon request.
4. Consistent with findings for borderline personality in Table 22.3, James and Taylor (2008) reported positive associations of borderline personality symptoms (assessed via self-report) with both internalizing and externalizing factors of psychopathology (assessed via computer-assisted interview). Notably, in this analysis, borderline personality operated more as an indicator of the anxious misery (distress) subfactor of internalizing than the fear disorder subfactor. However, the anxious misery and fear subfactors were highly correlated in this study (cf. Krueger, 1999b), and borderline personality symptoms evidenced significant bivariate relations with fear disorder symptoms. The implication is that borderline personality is related primarily to distress disorders and secondarily to fear disorders.

Acknowledgments

Preparation of this chapter was supported by Grant Nos. MH65137, MH072850, MH080239, and MH089727 from the National Institute of Mental Health. We are grateful to Greg Miller for his comments on an earlier version of this chapter.

References

Achenbach, T. M., & Edelbrock, C. S. (1978). The classification of child psychopathology: A review and analysis of empirical efforts. *Psychological Bulletin, 85*, 1275–1301.

Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A., et al. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia, 37*, 1111–1117.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

Anokhin, A. P., Vedeniapin, A. B., Sirevaag, E. J., Bauer, L. O., O'Connor, S. J., Kuperman, S., et al. (2000). The P300 brain potential is reduced in smokers. *Psychopharmacology, 149*, 409–413.

Arrindell, W. A., Emmelkamp, P. M. G., & van der Ende, J. (1984). Phobic dimensions: I. Reliability and generalizability across samples, gender, and nations. *Advances in Behavior Research and Therapy, 6*, 207–254.

Attou, A., Figiel, C., & Timsit-Berthier, M. (2001). ERP assessment of heroin detoxification and methadone treatment in chronic heroin users. *Clinical Neurophysiology, 31*, 171–180.

Barch, D. M., Carter, C. S., Braver, T. S., Sabb, F. W., MacDonald, A. W., Noll, D. C., et al. (2001). Selective deficits in prefrontal cortex function in medication naïve patients with schizophrenia. *Archives of General Psychiatry, 58*, 280–288.

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

Bauer, L. O., & Hesselbrock, V. M. (1999a). P300 decrements in teenagers with conduct problems: Implications for substance abuse risk and brain development. *Biological Psychiatry, 46,* 263–272.

Bauer, L. O., & Hesselbrock, V. M. (1999b). Subtypes of family history and conduct disorder: Effects on P300 during the Stroop test. *Neuropsychopharmacology, 21,* 51–62.

Bauer, L. O., O'Connor, S., & Hesselbrock, V. M. (1994). Frontal P300 decrements in antisocial personality disorder. *Alcoholism: Clinical and Experimental Research, 18,* 1300–1305.

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

Benning, S. D., Patrick, C. J., Blonigen, D. M., Hicks, B. M., & Iacono, W. G. (2005). Estimating facets of psychopathy from normal personality traits: A step toward community-epidemiological investigations. *Assessment, 12,* 3–18.

Benning, S. D., Patrick, C. J., Hicks, B. M., Blonigen, D. M., & Krueger, R. F. (2003). Factor structure of the Psychopathic Personality Inventory: Validity and implications for clinical assessment. *Psychological Assessment, 15,* 340–350.

Benning, S. D., Patrick, C. J., & Iacono, W. G. (2005). Psychopathy, startle blink modulation, and electrodermal reactivity in twin men. *Psychophysiology, 42,* 753–762.

Bernat, E., Patrick, C. J., Benning, S. D., & Tellegen, A. (2006). Thematic content and affective intensity: Modulation of startle reflex, electromyogram, heart rate, and skin conductance. *Psychophysiology, 43,* 93–103.

Bernat, E. M., Nelson, L. D., Steele, V. R., Patrick, C. J., & Gehring, W. J. (2010). *Externalizing psychopathology and gain/loss feedback in a simulated gambling task: Dissociable components of brain response revealed by time-frequency analysis.* Manuscript submitted for publication.

Bernat, E. M., Patrick, C. J., Cadwallader, M., van Mersbergen, M., & Seo, D. (2003). Affective orienting responses: A novelty P3 study with emotional pictures. *Psychophysiology, 40,* S25.

Bernat, E. M., Williams, W. J., & Gehring, W. J. (2005). Decomposing ERP time-frequency energy using PCA. *Clinical Neurophysiology, 116,* 1314–1334.

Biggins, C. A., MacKay, S., Clark, W., & Fein, G. (1997). Event-related potential evidence for frontal cortex effects of chronic cocaine dependence. *Biological Psychiatry, 42,* 472–485.

Bishop, S. J., Duncan, J., & Lawrence, A. D. (2004). State anxiety modulation of the amygdala response to unattended threat-related stimuli. *Journal of Neuroscience, 24,* 10364–10368.

Blair, R. J. R. (2006). Subcortical brain systems in psychopathy: The amygdala and associated structures. In C. J. Patrick (Ed.), *Handbook of psychopathy* (pp. 296–312). New York: Guilford Press.

Blair, R. J. R., Colledge, E., Murray, L., & Mitchell, D. G. (2001). A selective impairment in the processing of sad and fearful expressions in children with psychopathic tendencies. *Journal of Abnormal Child Psychology, 29,* 491–498.

Block, J., & Block, J. H. (1980). The role of ego-resiliency and ego-control in the organization of behavior. In W. A. Collins (Ed.), *Minnesota Symposium on Child Psychology* (Vol. 13, pp. 39–101). Hillsdale, NJ: Erlbaum.

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

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.

Bradley, M. M., Codispoti, M., Cuthbert, B. N., & Lang, P. J. (2001). Emotion and motivation: I. Defensive and appetitive reactions in picture processing. *Emotion, 1,* 276–298.

Brigham, J., Herning, R. I., & Moss, H. B. (1995). Event-related potentials and alpha synchronization in preadolescent boys at risk for psychoactive substance use. *Biological Psychiatry, 37,* 834–846.

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

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences, 4*, 215–222.

Buss, A. H., & Plomin, R. (1975). *A temperament theory of personality development*. New York: Wiley.

Buss, A. H., & Plomin, R. (1984). *Temperament: Early developing personality traits*. Hillsdale, NJ: Erlbaum.

Campbell, D. T., & Fiske, D. W. (1959). Convergent and discriminant validation by the multitrait–multimethod matrix. *Psychological Bulletin, 56*, 81–105.

Campbell, D. T., & Stanley, J. C. (1966). *Experimental and quasi-experimental designs for research*. Chicago: Rand McNally.

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.

Clark, L. A., Livesley, W. J., Schroeder, M. L., & Irish, S. (1996). The structure of maladaptive personality traits: Convergent validity between two systems. *Psychological Assessment, 8*, 294–303.

Clark, L. A., & Watson, D. (1999). Temperament: A new paradigm for trait psychology. In L. A. Pervin & O. John (Eds.), *Handbook of personality: Theory and research* (2nd ed., pp. 399–423). New York: Guilford Press.

Clark, L. A., Watson, D., & Reynolds, S. (1995). Diagnosis and classification of psychopathology: Challenges to the current system and future directions. *Annual Review of Psychology, 46*, 121–153.

Cleckley, H. (1976). *The mask of sanity* (5th ed.). St. Louis, MO: Mosby.

Cloninger, C. R. (1987). A systematic method for clinical description and classification of personality variants. *Archives of General Psychiatry, 44*, 573–588.

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.

Cook, E. W., III. (1999). Affective individual differences, psychopathology, and startle reflex modulation. In M. E. Dawson, A. M. Schell, & A. H. Boehmelt (Eds.), *Startle modification: Implications for clinical science, cognitive science, and neuroscience* (pp. 187–208). New York: Cambridge University Press.

Cook, E. W., III, Melamed, B. G., Cuthbert, B. N., McNeil, D. W., & Lang, P. J. (1988). Emotional imagery and the differential diagnosis of anxiety. *Journal of Consulting and Clinical Psychology, 56*, 734–740.

Corr, P. J., Kumari, V., Wilson, G. D., Checkley, S., & Gray, J. A. (1997). Harm avoidance and affective modulation of the startle reflex: A replication. *Personality and Individual Differences, 22*, 591–593.

Corr, P. J., Wilson, G. D., Fotiadou, M., Kumari, V., Gray, N. S., Checkley, S., et al. (1995). Personality and affective modulation of the startle reflex. *Personality and Individual Differences, 19*, 543–553.

Courchesne, E., Hillyard, S. A., & Galambos, R. (1975). Stimulus novelty, task relevance, and the visual evoked potential in man. *Electroencephalography and Clinical Neurophysiology, 39*, 131–143.

Curtin, J. J., Patrick, C. J., Lang, A. R., Cacioppo, J. T., & Birbaumer, N. (2001). Alcohol affects emotion through cognition. *Psychological Science, 12*, 527–531.

Cuthbert, B. N., Lang, P. J., Strauss, C., Drobes, D., Patrick, C. J., & Bradley, M. M. (2003). The psychophysiology of anxiety disorder: Fear memory imagery. *Psychophysiology, 40*, 407–422.

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

Davidson, R. J., Pizzigalli, D., Nitschke, J. B., & Putnam, K. M. (2002). Depression: Perspectives from affective neuroscience. *Annual Review of Psychology, 53*, 545–574.

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. (1979). Diazepam and flurazepam: Effects on conditioned fear as measured with the potentiated startle paradigm. *Psychopharmacology, 62*, 1–7.

Davis, M. (1989). Neural systems involved in fear-potentiated startle. *Annals of the New York Academy of Sciences, 563*, 165–183.

Davis, M. (1992). The role of the amygdala in conditioned fear. In J. Aggleton (Ed.), *The amygdala: Neurobiological aspects of emotion, memory and mental dysfunction* (pp. 255–305). New York: Wiley.

Davis, M., Falls, W. A., Campeau, S., & Kim, M. (1993). Fear-potentiated startle: A neural and

pharmacological analysis. *Behavioural Brain Research, 58*, 175–198.

Davis, M., Walker, D. L., & Lee, Y. (1997). Roles of the amygdala and bed nucleus of the stria terminalis in fear and anxiety measured with the acoustic startle reflex. *Annals of the New York Academy of Sciences, 831*, 305–331.

Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a neural system for error detection and compensation. *Psychological Science, 5*(5), 303–305.

Depue, R. A., & Iacono, W. G. (1989). Neurobehavioral aspects of affective disorders. *Annual Review of Psychology, 40*, 457–492.

Depue, R. A., Luciana, M., Arbisi, P., Collins, P., & Leon, A. (1994). Dopamine and the structure of personality: Relation of agonist-induced dopamine activity to positive emotionality. *Journal of Personality and Social Psychology, 67*, 485–498.

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

Dien, J., Spencer, K. M., & Donchin, E. (2003). Localization of the event-related potential novelty response as defined by principal components analysis. *Cognitive Brain Research, 17*(3), 637–650.

Dikman, Z. V., & Allen, J. J. (2000). Error monitoring during reward and avoidance learning in high- and low-socialized individuals. *Psychophysiology, 37*(1), 43–54.

Ding, L., Wilke, C., Xu, B., Xu, X., van Drongelen, W., Kohrman, M., et al. (2007). EEG source imaging: Correlating source locations and extents with electrocorticography and surgical resections in epilepsy patients. *Journal of Clinical Neurophysiology, 24*, 130–136.

Dvorak-Bertsch, J. D., Curtin, J. J., Rubinstein, T. J., & Newman, J. P. (2007). Anxiety moderates the interplay between cognitive and affective processing. *Psychological Science, 18*, 699–705.

Ericsson, K., & Kinsch, W. (1995). Long-term working memory. *Psychological Review*, 102(2), 211–245.

Eysenck, H. J. (1967). *The biological basis of personality*. Springfield, IL: Thomas.

Falconer, D. S. (1989). *Introduction to quantitative genetics* (3rd ed.). New York: Wiley.

Fanselow, M. S. (1994). Neural organization of the defensive behavior system responsible for fear. *Psychonomic Bulletin and Review, 1*, 429–438.

First, M., Spitzer, R., Gibbon, M., & Williams, J. (1997). *Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II)*. Washington, DC: American Psychiatric Press.

Flor, H., Birbaumer, N., Hermann, C., Ziegler, S., & Patrick, C. J. (2002). Aversive Pavlovian conditioning in psychopaths: Peripheral and central correlates. *Psychophysiology, 39*, 505–518.

Fowles, D. C., & Dindo, L. A (2006). Dual-deficit model of psychopathy. In C. J. Patrick (Ed.), *Handbook of psychopathy* (pp. 14–34). New York: Guilford Press.

Gehring, W. J., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1995). A brain potential manifestation of error-related processing. In G. Karmos, M. Molnar, V. Csepe, I. Czigler, & J. E. Desmedt (Eds.), *Perspectives of event-related potentials research* (pp. 267–272). Amsterdam: Elsevier.

Goldsmith, H. H., & Campos, J. J. (1982). Toward a theory of infant temperament. In R. N. Emde & R. J. Harmon (Eds.), *The development of attachment and affiliative systems* (pp. 161–193). New York: Plenum Press.

Goldsmith, H. H., Lemery, K. S., Buss, K. A., & Campos, J. J. (1999). Genetic analyses of focal aspects of infant temperament. *Developmental Psychology, 35*, 972–985.

Gorenstein, E. E., & Newman, J. P. (1980). Disinhibitory psychopathology: A new perspective and a model for research. *Psychological Review, 87*, 301–315.

Gough, H. G. (1960). Theory and measurement of socialization. *Journal of Consulting Psychology, 24*, 23–30.

Gotlib, I. H., Sivers, H., Gabrieli, J. D. E., Whitfield-Gabrieli, S., Goldin, P., Minor, K. L., et al. (2005). Subgenual anterior cingulate activation to valenced emotional stimuli in major depression. *NeuroReport, 16*, 1731–1734.

Gray, J. A. (1991). Neural systems, emotion and personality. In J. Madden (Ed.), *Neurobiology of learning, emotion and affect* (pp. 273–306). New York: Raven Press.

Grillon, C., & Baas, J. (2003). A review of the modulation of the startle reflex by affective states and its application in psychiatry. *Clinical Neurophysiology, 114*, 1557–1579.

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

Hamm, A. O., Cuthbert, B. N., Globisch, J., &

Vaitl, D. (1997). Fear and the startle reflex: Blink modulation and autonomic response patterns in animal and mutilation fearful subjects. *Psychophysiology, 34*, 97–107.

Harari, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297*, 400–403.

Hare, R. D. (1978). Electrodermal and cardiovascular correlates of psychopathy. In R. D. Hare & D. Schalling (Eds.), *Psychopathic behavior: Approaches to research* (pp. 107–143). Chichester, UK: Wiley.

Hare, R. D. (1991). *The Hare Psychopathy Checklist—Revised.* Toronto: Multi-Health Systems.

Hare, R. D. (2003). *The Hare Psychopathy Checklist—Revised* (2nd ed.). Toronto: Multi-Health Systems.

Hare, R. D., Harpur, T. J., Hakstian, A. R., Forth, A. E., Hart, S. D., & Newman, J. P. (1990). The Revised Psychopathy Checklist: Reliability and factor structure. *Psychological Assessment, 2*, 338–341.

Harpur, T. J., Hakstian, A. R., & Hare, R. D. (1988). Factor structure of the Psychopathy Checklist. *Journal of Consulting and Clinical Psychology, 56*, 741–747.

Harpur, T. J., Hare, R. D., & Hakstian, A. R. (1989). Two-factor conceptualization of psychopathy: Construct validity and assessment implications. *Psychological Assessment, 1*, 6–17.

Heller, W., & Nitschke, J. (1998). The puzzle of regional brain activity in anxiety and depression: The importance of subtypes and comorbidity. *Cognition and Emotion, 12*, 421–447.

Heller, W., Nitschke, J., Etienne, M. A., & Miller, G. A. (1997). Patterns of regional brain activity differentiate types of anxiety. *Journal of Abnormal Psychology, 106*, 376–385.

Hettema, J. M., Anna, P., Neale, M., Kendler, K. A., & Fredrikson, M. (2003). A twin study of the genetics of fear conditioning. *Archives of General Psychiatry, 60*, 702–708.

Hicks, B. M., Bernat, E. M., Malone, S. M., Iacono, W. G., Patrick, C. J., Krueger R. F., et al. (2007). Genes mediate the association between P3 amplitude and externalizing disorders. *Psychophysiology, 44*, 98–105.

Hicks, B. M., & Patrick, C. J. (2006). Psychopathy and negative emotionality: Analyses of suppressor effects reveal distinct relations with emotional distress, fearfulness, and anger–hostility. *Journal of Abnormal Psychology, 115*, 276–287.

Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review, 109*, 679–709.

Holroyd, C. B., Dien, J., & Coles, M. G. (1998). Error-related scalp potentials elicited by hand and foot movements: Evidence for an output-independent error-processing system in humans. *Neuroscience Letters, 242*(2), 65–68.

Holroyd, C. B., Larsen, J. T., & Cohen, J. D. (2004). Context dependence of the event-related brain potential associated with reward and punishment. *Psychophysiology, 41*(2), 245–253.

Hyman, S. M. (2007). Can neuroscience be integrated into the DSM-V? *Nature Reviews Neuroscience, 8*, 725–732.

Iacono, W. G. (1991). Psychophysiological assessment of psychopathology. *Psychological Assessment, 3*, 309–320.

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

Insel, T. R., & Scolnick, E. M. (2006). Cure therapeutics and strategic prevention: Raising the bar for mental health research. *Molecular Psychiatry, 11*, 11–17.

Jackson, D. C., Mueller, C. J., Dolski, I., Dalton, K. M., Nitschke, J. B., Urry, H. L., et al. (2003). Now you feel it, now you don't: Frontal EEG asymmetry and individual differences in emotion regulation. *Psychological Science, 14*, 612–617.

James, L. M., & Taylor, J. (2008). Revisiting the structure of mental disorders: Borderline personality disorder and the internalizing/externalizing spectra. *British Journal of Clinical Psychology, 47*, 361–380.

James, W. (1983). *The principles of psychology.* Cambridge, MA: Harvard University Press. (Original work published 1890)

Jiang, Y., & He, S. (2006) Cortical responses to invisible faces: Dissociating subsystems for facial-information processing. *Current Biology, 16*, 2023–2029.

Jiang, Y., Shannon, R. W., Vizueta, N., Bernat, E. M., Patrick, C. J., & He, S. (2009). Dynamics of processing invisible faces in the brain: Automatic neural encoding of facial expression information. *NeuroImage, 44*, 1171–1177.

Junghoefer, M., Bradley, M. M., Elbert, T. R., & Lang, P. J. (2001). Fleeting images: A new look at early emotion discrimination. *Psychophysiology, 38*, 175–178.

Kagan, J. (1994). *Galen's prophecy: Temperament in human nature*. New York: Basic Books.

Kagan, J., & Snidman, N. (1999). Early childhood predictors of adult anxiety disorders. *Biological Psychiatry, 46*, 1536–1541.

Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). 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.

Kochanska, G. K. (1997). Multiple pathways to conscience for children with different temperaments: From toddlerhood to age 5. *Developmental Psychology, 33*, 228–240.

Kramer, M. D., Patrick, C. J., Krueger, R. F., & Bayevsky, M. (2010). *Phenotypic and etiologic parallels in the structure of fear and fearlessness*. Manuscript submitted for publication.

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

Krueger, R. F. (1999b). The structure of common mental disorders. *Archives of General Psychiatry, 56*, 921–926.

Krueger, R. F. (2005). Continuity of Axes I and II: Toward a unified model of personality, personality disorders, and clinical disorders. *Journal of Personality Disorders, 19*, 233–261.

Krueger, R. F., Hicks, B. M., Patrick, C. J., Carlson, S. R., 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.

Krueger, R. F., Skodol, A. E., Livesley, W. J., Shrout, P., & Huang, Y. (2007). Synthesizing dimensional and categorical approaches to personality disorders: Refining the research agenda for DSM-V Axis II. *International Journal of Methods in Psychiatric Research, 16*, S65–S73.

Lang, P. J. (1995). The emotion probe: Studies of motivation and attention. *American Psychologist, 50*, 372–385.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review, 97*, 377–395.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). Motivated attention: Affect, activation, and action. In P. J. Lang, R. F. Simons, & M. T. Balaban (Eds.), *Attention and orienting: Sensory and motivational processes* (pp. 97–135). Hillsdale, NJ: Erlbaum.

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

Levenston, G. K., Patrick, C. J., Bradley, M. M., & Lang, P. J. (2000). The psychopath as observer: Emotion and attention in picture processing. *Journal of Abnormal Psychology, 109*, 373–385.

Lilienfeld, S. O., & Andrews, B. P. (1996). Development and preliminary validation of a self report measure of psychopathic personality traits in noncriminal populations. *Journal of Personality Assessment, 66*, 488–524.

Lissek, S., & Powers, A. S. (2003). Sensation seeking and startle modulation by physically threatening images. *Biological Psychology, 63*, 179–197.

Livesley, W. J., Schroeder, M. L., Jackson, D. N., & Jang, K. L. (1994). Categorical distinctions in the study of personality disorder: implications for classification. *Journal of Abnormal Psychology, 103*, 6–17.

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

Lykken, D. T. (1957). A study of anxiety in the sociopathic personality. *Journal of Abnormal and Clinical Psychology, 55*, 6–10.

Lykken, D. T. (1995). *The antisocial personalities*. Mahwah, NJ: Erlbaum.

Maher, B. (1968). *Principles of psychopathology: An experimental approach*. New York: McGraw-Hill.

Mars, R. B., Coles, M. G., Grol, M. J., Holroyd, C. B., Nieuwenhuis, S., Hulstijn, W., et al. (2005). Neural dynamics of error processing in medial frontal cortex. *NeuroImage, 28*(4), 1007–1013.

Marsh, A. A., Finger, E. C., Mitchell, G. V., Reid, M. E., Sims, C., Kosson, D. S., et al. (2008). Reduced amygdala response to fearful expressions in children and adolescents with callous–unemotional traits and disruptive behavior

disorders. *American Journal of Psychiatry, 165*, 712–720.

McGhie, A., & Chapman, J. (1961). Disorders of attention and perception in early schizophrenia. *British Journal of Medical Psychology, 34*, 103–116.

Meehl, P. E. (1990). Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *Journal of Personality Disorders, 4*, 1–99.

Melzig, C. A., Weike, A. I., Zimmermann, J., & Hamm, A. O. (2007). Startle reflex modulation and autonomic responses during anxious apprehension in panic disorder patients. *Psychophysiology, 45*, 846–854.

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

Miller, E. K., & Cohen, J. D. (2001). Integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*(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.

Mineka, S., Watson, D., & Clark, L. E. A. (1998). Comorbidity of anxiety and unipolar mood disorders. *Annual Review of Psychology, 49*, 377–412.

Molto, J., Poy, R., Segarra, P., Pastor, M. C., & Montanes, S. (2007). Response perseveration in psychopaths: Interpersonal/affective or social deviance traits? *Journal of Abnormal Psychology, 116*, 632–637.

Morey, L. C., Gunderson, J., Quigley, B. D., & Lyons M. (2000). Dimensions and categories: The "Big Five" factors and the DSM personality disorders. *Assessment, 7*, 203–216.

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.

Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., et al. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature, 383*, 812–815.

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus–norepinephrine system. *Psychological Bulletin, 131*(4), 510–532.

Nye, F. I., & Short, J. F., Jr. (1957). Scaling delinquent behavior. *American Sociological Review, 22*, 326–331.

Öhman, A., & Soares, J. J. F. (1994). "Unconscious anxiety": Phobic responses to masked stimuli. *Journal of Abnormal Psychology, 103*, 231–240.

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*(1), 84–95.

Patrick, C. J. (1994). Emotion and psychopathy: Startling new insights. *Psychophysiology, 31*, 319–330.

Patrick, C. J. (2007). Antisocial personality disorder and psychopathy. In W. O'Donohue, K. A. Fowler, & S. O. Lilienfeld (Eds.), *Handbook of personality disorders* (pp. 109–166). New York: Sage.

Patrick, C. J., & Bernat, E. (2006). The construct of emotion as a bridge between personality and psychopathology. In R. F. Krueger & J. Tackett (Eds.), *Personality and psychopathology* (pp. 174–209). New York: Guilford Press.

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

Patrick, C. J., & Bernat, E. M. (2009a). 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. (2009b). Neurobiology of psychopathy: A two-process theory. In G. G. Berntson & J. T. Cacioppo (Eds.), *Handbook of neuroscience for the behavioral sciences* (pp. 1110–1131). Hoboken, NJ: Wiley.

Patrick, C. J., Berthot, B., & Moore, J. D. (1996). Diazepam blocks fear-potentiated startle in humans. *Journal of Abnormal Psychology, 105*, 89–96.

Patrick, C. J., Bradley, M. M., & Lang, P. J. (1993). Emotion in the criminal psychopath: Startle reflex modulation. *Journal of Abnormal Psychology, 102*, 82–92.

Patrick, C. J., Fowles, D. C., & Krueger, R. F. (2009). Triarchic conceptualization of psychopathy: Developmental origins of disinhibi-

tion, boldness, and meanness. *Development and Psychopathology, 21*(3), 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., & Lang, A. R. (1999). Psychopathic traits and intoxicated states: Affective concomitants and conceptual links. In M. E. Dawson, A. M. Schell, & A. H. Bohmelt (Eds.), *Startle modification: Implications for neuroscience, cognitive science, and clinical science* (pp. 209–230). New York: Cambridge University Press.

Patterson, C. M., & Newman, J. P. (1993). Reflectivity and learning from aversive events: Toward a psychological mechanism for the syndromes of disinhibition. *Psychological Review, 100*, 716–736.

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.

Polich, J., Pollock, V. E., & Bloom, F. E. (1994). Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psychological Bulletin, 115*, 55–73.

Porjesz, B., Begleiter, H., & Garozzo, R. (1980). Visual evoked potential correlates of information processing deficits in chronic alcoholics. In H. Begleiter (Ed.), *Biological effects of alcohol* (pp. 603–623). New York: Plenum Press.

Ridderinkhoff, K. R., de Vlugt, Y., Bramlage, A., Spaan, M., Elton, M., Snel, J., et al. (2002). Alcohol consumption impairs detection of performance errors in mediofrontal cortex. *Science, 298*, 2209–2211.

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

Rosen, J. B., & Schulkin, J. (1998). From normal fear to pathological anxiety. *Psychological Review, 105*, 325–350.

Rothbart, M. K. (1981). Measurement of temperament in infancy. *Child Development, 52*, 569–578.

Rothbart, M. K., & Ahadi, S. A. (1994). Temperament and the development of personality. *Journal of Abnormal Psychology, 103*, 55–66.

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

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants grown up: Adult amygdalar response to novelty. *Science, 300*, 1952–1953.

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

Sellbom, M., Ben-Porath, Y. S., & Bagby, R. M. (2008). On the hierarchical structure of mood and anxiety disorders: Confirmatory evidence and an elaborated model of temperament markers. *Journal of Abnormal Psychology, 117*, 576–590.

Siever, L. J. (2000). Genetics and neurobiology of personality disorders. *European Psychiatry, 15*, 54–57.

Siever, L. J., & Davis, K. L. (1991). A psychobiological perspective on the personality disorders. *American Journal of Psychiatry, 148*, 1647–1658.

Skinner, A. (1982). The Drug Abuse Screening Test. *Addictive Behaviors, 7*, 363–371.

Skinner, H. A., & Allen, B. A. (1982). Alcohol dependence syndrome: Measurement and validation. *Journal of Abnormal Psychology, 91*, 199–209.

Spencer, K. M., Dien, J., & Donchin, E. (1999). A componential analysis of the ERP elicited by novel events using a dense electrode array. *Psychophysiology, 36*(3), 409–414.

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. (1982). *Brief manual for the Multidimensional Personality Questionnaire.* Unpublished manuscript, University of Minnesota.

Tellegen, A. (1985). Structures of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In A. H. Tuma & J. D. Maser (Eds.), *Anxiety and the anxiety disorders* (pp. 681–706). Hillsdale, NJ: Erlbaum.

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. II. Personality measurement and testing* (pp. 261–292). London: Sage.

Trull, T. J. (1992). DSM-IIIR personality disorders and the five-factor model of personality: An empirical comparison. *Journal of Abnormal Psychology, 101*, 553–560.

Trull, T. J., & Sher, K. J. (1994). Relationship between the five-factor model of personality and Axis I disorders in a nonclinical sample. *Journal of Abnormal Psychology, 103*, 350–360.

Vaidyanathan, U., Patrick, C. J., & Bernat, E. M. (2009). Startle reflex potentiation during aversive picture viewing as an index of trait fear. *Psychophysiology, 46*, 75–85.

Venables, N., Reich, E., Bernat, E. M., Hall, J. R., & Patrick, C. J. (2008). Reduced P300 amplitude in criminal psychopathy is related to externalizing tendencies. *Psychophysiology, 45*, S46.

Verona, E., Patrick, C. J., & Joiner, T. E. (2001). Psychopathy, antisocial personality, and suicide risk. *Journal of Abnormal Psychology, 110*, 462–470.

Vollebergh, W. A. M., Iedema, J., Bijl, R. V., de Graaf, R., Smit, F., & Ormel, J. (2001). The structure and stability of common mental disorders: The NEMESIS Study. *Archives of General Psychiatry, 58*, 597–603.

Vrana, S. R., Constantine, J. A., & Westman, J. S. (1992). Startle reflex modulation as an outcome measure in the treatment of phobia: Two case studies. *Behavioral Assessment, 14*, 279–291.

Vul, E., Harris, C., Winkielman, P., & Pashler, H. (2009). Puzzlingly high correlations in fMRI studies of emotion, personality, and social cognition. *Perspectives on Psychological Science, 4*, 274–290.

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

Watson, D. (2005). Rethinking the mood and anxiety disorders. *Journal of Abnormal Psychology, 114*, 522–536.

Watson, D., O'Hara, M. W., Simms, L. J., Kotov, R., Chmielewski, M., Montez, E., et al. (2007). Development and validation of the Inventory for Depression and Anxiety Symptoms. *Psychological Assessment, 19*, 253–268.

Whalen, P. J. (1998). Fear, vigilance and ambiguity: Initial neuroimaging studies of the human amygdala. *Current Directions in Psychological Science, 7*, 177–188.

Widiger, T. A., & Sanderson, C. J. (1995). Towards a dimensional model of personality disorders in DSM-IV and DSM-V. In W. J. Livesley (Ed.), *The DSM-IV personality disorders* (pp. 433–458). New York: Guilford Press.

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

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.

Zuckerman, M. (1979). *Sensation seeking: Beyond the optimal level of arousal.* Hillsdale, NJ: Erlbaum.

Zuckerman, M. (1999). *Vulnerability to psychopathology: A biosocial model.* Washington, DC: American Psychological Association.