

The Externalizing Spectrum: Structure and Mechanisms

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## Overview

This chapter introduces a psychobiological construct that is central to adult personality and psychopathology, the externalizing factor. We conceptualize externalizing as a broad vulnerability dimension that underlies and links psychopathological syndromes involving antisocial behavior and substance dependence, as well as personality traits reflecting impulsivity and disinhibition. Because of its relevance to diverse behaviors with high social impact, ranging from violence to illicit substance dependence, elucidating the nature and psychobiology of the externalizing dimension is fundamental to understanding, and ultimately to curbing, these costly behaviors.

We conceive of the externalizing factor as an underlying trait dimension that reflects vulnerability to various forms of disorder. It is manifested at the overt behavioral level by disinhibitory actions and symptoms, and at the personality level by traits of impulsiveness and spontaneity, stimulation seeking, and rebellious nonconformity. We propose that these personality traits and overt behavioral indicators are associated with deviations in neuro-cognitive processing that more directly reflect the underlying biological basis of the externalizing vulnerability factor.

Recent research indicates that the amplitude of the P300 component of the cortical event-related potential (ERP) provides a biological marker of externalizing vulnerability. However, a limitation of this brain response indicator is that it is diffusely generated (REFS), and thus the underlying basis and functional implications of reduced P300 amplitude remain unclear (Begleiter & Porjesz, 1999; Iacono et al., 2002). We therefore call for systematic cognitive neuroscience research on specific brain regions underlying the broad externalizing factor, with an emphasis on anterior “executive-control” systems. Pharmacologic manipulations that disinhibit behavior can provide a useful laboratory model for studying processing underlying externalizing. As an example of this, we describe recent alcohol challenge studies examining brain response deviations associated with deficits in cognitive control and behavioral performance under conditions of intoxication.

## Conceptual Framework

Psychopathologic syndromes do not typically occur in isolation within affected persons. Instead, they routinely co-occur with symptoms of other disorders. For example, patients diagnosed with depression frequently meet criteria for a concurrent anxiety disorder, and individuals diagnosed with antisocial personality disorder commonly exhibit co-occurring substance use problems. Furthermore, this comorbidity among disorders is systematic rather than random, i.e., the presence of one disorder predicts the occurrence of other specified disorders at levels well above population base rates (REFS). The question of which diagnostic syndromes occur most reliably with which others was investigated by Krueger (1999) using adult diagnostic data from the National Comorbidity Survey (Kessler et al., 1994). Krueger performed a quantitative structural analysis of the most common Axis I disorders within the DSM and found two broad, latent factors that accounted for the covariance among these various disorders: an externalizing factor encompassing antisocial personality disorder, alcohol dependence, and drug dependence, and an internalizing dimension encompassing mood and anxiety disorders (see also Krueger, Caspi, Moffitt, & Silva, 1998; Vollebergh, Iedema, Bijl, de Graaf, Smit, Ormel, 2001). This research demonstrates a coherent structure to the comorbidity among diagnostic syndromes and implies that subgroups of mental disorders within the DSM are connected at some basic level.

Our focus in the current chapter is the broad dimension that connects antisocial deviance and substance use disorders—the externalizing (EXT) factor. Our work is framed in terms of a *hierarchical spectrum model* of externalizing psychopathology. The model includes a higher-order factor that reflects general risk for externalizing problems, and lower-order syndrome variables that represent specific behavioral expressions of this broad risk factor (i.e., conduct disorder, adult antisocial behavior, alcohol dependence, drug dependence). The broad EXT factor represents the common variance among the varying distinct syndromes within the spectrum, and it is presumed that there are etiologic influences that contribute directly to this common factor. Thus, the model allows for causal variables that are general in

their impact, i.e., etiologic influences that contribute to risk for multiple disorders within the spectrum, via their influence on the broad externalizing factor. At the same time, the model incorporates etiologic influences that are specific to distinct disorders within the spectrum.

In this way, the hierarchical model provides for reconciliation between a “lumping” perspective, in which varying disorders are considered as variants of a single broad class of psychopathology, and a “splitting” perspective, in which these disorders are regarded to be separate entities. Both perspectives receive support from the existing literature. For example, the genetic risk for disorders and traits within the externalizing spectrum is neither highly specific (Bohman, Sigvardsson, & Cloninger, 1981; Cadoret, O’Gorman, Troughton, & Heywood, 1985; Cadoret, Troughton, & O’Gorman 1987; Cloninger, Bohman, & Sigvardsson, 1981; Crowe, 1974; Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973), nor highly nonspecific (Grove et al., 1990; Jang, Vernon, & Livesley, 2000; Pickens, Svikis, McGue, & LaBuda, 1995; Slutske et al., 1998). Thus, the existing literature is most compatible with a model that recognizes both commonalities and distinctions among disorders within the externalizing spectrum. Our model incorporates the idea that specific syndromes within the externalizing spectrum are continuous, correlated elements, or facets, of the overarching externalizing trait factor. Rather than focusing research on specific syndromes, the hierarchical spectrum model encourages investigation of both specific and general etiological factors within the externalizing domain.

#### Modeling the Externalizing Spectrum and its Etiologic Determinants

Multivariate analyses of phenotypic, observed correlations among mental disorders reveal a broad, latent factor or dimension linking substance dependence and antisocial behavior disorders in late-adolescence and adulthood. Following the terminology used in research that has examined the structure of emotional and behavioral problems in children (Achenbach & Edelbrock, 1978, 1984), we use the label externalizing for this broad dimension (Kendler, Davis, & Kessler, 1997; Krueger et al., 1998; Krueger, 1999). The existing twin literature suggests a genetic basis for the externalizing factor, as evidence has

accumulated for close genetic connections among pairs of disorders within the externalizing spectrum (Grove et al., 1990; Jang, Vernon, & Livesley, 2000; Slutske et al., 1998). Young, Stallings, Corley, Krauter, & Hewitt, (2000) examined genetic and environmental contributions to this latent dimension, defined as the common factor linking child-reported symptoms of conduct disorder, attention-deficit hyperactivity disorder, substance experimentation (number of substances used on more than five occasions) and the personality trait of novelty seeking in 334 twin pairs aged 12-18. Their analysis revealed that the majority of variance (85%) in the latent externalizing dimension was attributable to genetic influences.

Notably, the externalizing dimension accounts only for the shared variance among substance dependence and antisocial behavior disorders. When this common variance is accounted for, significant variance remains uniquely associated with each disorder (Krueger, 1999; Krueger et al., 1998). Moreover, in comparison with findings from twin studies cited above, adoption studies have indicated greater genetic specificity for antisocial behavior and substance use disorders (Bohman, Sigvardsson, & Cloninger, 1981; Cadoret, O'Gorman, Troughton, & Heywood, 1985; Cadoret, Troughton, & O'Gorman 1987; Cloninger, Bohman, & Sigvardsson, 1981; Crowe, 1974; Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973). These contrasting observations might be reconciled if at least a portion of the variance unique to each externalizing syndrome were found to reflect specific causal determinants, distinct from the etiology of the broad externalizing dimension. If the unique part of each individual disorder were shown to have etiologic determinants distinct from those of the broad externalizing factor, then lumping and splitting positions could be reconciled. Rather than arguing for strict etiologic generality versus specificity, such data would instead support a hierarchical conceptualization of the externalizing disorders as described above.

Evidence in support of this conceptualization was provided by a recent multivariate behavior genetic analysis of disorders within the externalizing spectrum undertaken by our research group (Krueger,

Hicks, Patrick, Carlson, Iacono, and McGue, 2002). This study utilized data from the Minnesota Twin-Family Study, a birth record based epidemiological study of monozygotic (MZ) and dizygotic (DZ) twins born in the state of Minnesota (Iacono, Carlson, Taylor, Elkins, & McGue, 1999). Twins and their mothers were interviewed in person to assess the twins' antisocial behavior (both child/adolescent and adult forms) and alcohol and illicit substance dependence. Scores on a self-report measure of traits related to impulsiveness, sensation-seeking, and rebelliousness, the higher-order Constraint (CON) scale of Tellegen's (in press) Multidimensional Personality Questionnaire (MPQ), were also included in the analysis to test for an etiologic connection between disinhibited personality and externalizing psychopathology (cf. Sher & Trull, 1994; Justus, Finn, & Steinmetz, 2001; Young et al., 2000).

The fit of a model postulating that these varying symptom and personality measures operate as indicators of a latent externalizing dimension was evaluated. Additionally, the fact that the participant sample consisted of MZ and DZ twins allowed us to extend the existing literature by modeling genetic and environmental influences on both the externalizing dimension, and the unique, residual variance in each of the measured indicators of this underlying dimension. A behavior genetic model called the common pathway model (Neale & Cardon, 1992; Waldman & Slutske, 2000) provides such a test. This model allows for additive genetic (A), shared environmental (C), and non-shared environmental (E) influences on both the latent externalizing dimension, and the residual variance in each indicator of this dimension. To investigate the possibility of gender differences in structure and etiology, we compared the fit of sex variant and sex invariant common pathway models to the data. The sex variant model allowed parameters to differ for males and females while the sex invariant model constrained the parameters to be equal for males and females. For the sex variant model,  $\chi^2 = 184.14$ ,  $df = 76$ , Root Mean Squared Error of Approximation (RMSEA) = .020. For the sex invariant model,  $\chi^2 = 216.61$ ,  $df = 98$ , RMSEA = .025. RMSEA values for both models were less than .05 indicating the common pathway model provides a very good fit to the data (Browne & Cudeck, 1993). The likelihood ratio chi square test comparing the models

was not significant,  $\Delta\chi^2 = 32.47$ ,  $df = 22$ ,  $p > .05$ , indicating the parameter estimates did not differ significantly by sex.

Figure 1 depicts the standardized parameter estimates and 95% confidence intervals around zero for the sex invariant common pathway model. The path coefficients in the figure can be squared to yield the percentage of variance contributed by a given path. Thus, additive genetic (A) influences accounted for 81% (.90 x .90) of the variance of the latent externalizing factor; the remaining variance in this common factor (.43 X .43, or 19%) was attributable to non-shared environmental (E) influences. All of the disorder variables had strong and significant loadings on Externalizing: AAB (adult antisocial behavior) = .78, CD (conduct disorder) = .58, ALD (alcohol dependence) = .71, DD (drug dependence) = .63. The personality variable, rCON (MPQ Constraint, reverse-scored so that higher scores reflect greater disinhibition) had a somewhat lower, albeit highly significant loading (= .47) on the Externalizing factor—probably due to unique method variance (cf. Campbell & Fiske, 1959) associated with the distinct domain in which personality was assessed (i.e., self-report, versus in-person clinical interview for the symptom variables).

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Latent variables at the bottom of Figure 1 are specific or residual ACE effects: etiologic influences that contribute to the expression of a particular indicator variable but not to the expression of any other observed phenotype in the model. As such, specific ACE effects are etiologic influences that contribute to differences among the observed indicator variables. The common pathway model describes how these specific effects lead to the different phenotypic expressions of the underlying externalizing dimension. Reversed CON is the only variable for which the specific A loading (.61) was significant, indicating that there are genetic effects that contribute to the expression of CON independently of

Externalizing. While the specific A loadings were not significant for any of the disorders, the confidence intervals for these variables are relatively large, with the exception of AAB. CD is the only variable for which the specific C loading (.51) was significant, indicating that there are shared environmental effects that are unique to the expression of CD. Specific E effects were significant for all the observed variables: AAB = .62, CD = .58, ALD = .57, DD = .63, reversed CON = .64. These data indicate that there are non-shared environmental effects specific to the expression of a given variable and to the differentiation of that variable from the other variables included in the model.

The findings of this genetic structural analysis provide support for a hierarchical spectrum model of these syndromes and traits by demonstrating substantial heritability of the overarching externalizing dimension, as well as distinctive etiological contributions to specific, distinctive syndromes within the spectrum. The hierarchical model views individual diagnostic syndromes as arising from broad as well as specific causal influences. The model posits the existence of a broad, highly heritable trait disposition (EXT) that confers a vulnerability to the development of any of these disorders. However, the expression of this vulnerability in terms of one syndrome or another is shaped by causal influences that are specific to that diagnostic entity. Thus, the hierarchical model conceives of individual disorders as facets of externalization—alternative manifestations of a broader psychopathologic process—rather than as wholly separate entities. In this way, the model explicitly accommodates the phenomenon of comorbidity among disorders while recognizing distinctions across disorders.

From this perspective, the broad EXT factor represents a novel and important target for research on psychopathology. Establishing what this common factor represents in behavioral and biological terms will advance our understanding of how externalizing syndromes develop and why certain persons are at risk for developing them. Historically, research on the externalizing disorders has focused on individuals who meet criteria for a single diagnosis (i.e., “pure cases”) as a means of isolating specific etiologic influences. However, individuals with multiple disorders are also important to study because they

represent the high pole of the vulnerability factor that these disorders share. The above-mentioned work indicates that child and adult antisocial deviance, as well as alcohol and drug problems, are alternative manifestations (facets) of this underlying vulnerability. Individuals high on the EXT vulnerability dimension are likely to exhibit severe symptoms of these, and potentially other, disorders. The next section considers other problem behaviors and syndromes that appear to be linked to the externalizing construct. A further point is that the high heritability of EXT makes it a logical referent in the search for neurobiological indicators of vulnerability to disorders of this type. In the section that follows, we briefly review empirical data indicating that reduced P300 brain response amplitude may be one such indicator.

#### Other Probable Facets of Externalizing

A key point of the hierarchical model is that a broad range of problem behaviors involving behavioral dysregulation and addictions can be seen as arising from a common underlying vulnerability factor (EXT). In this section, we briefly consider other behavior problems that might be considered expressions (facets) of this underlying vulnerability.

Reactive aggression and impulsive suicide. A large research literature substantiates a link between the phenomena encompassed by EXT (i.e., antisociality, substance dependence, and disinhibitory traits) and aggressive behavior, particularly of the reactive-impulsive type (Patrick & Zempolich, 1998; Patrick et al., 1997), and also suicidal behavior (Verona & Patrick, 2000; Verona et al., in press). Extreme antisociality, reactive violence, and impulsive suicidal behavior also share a common biological marker in the form of reduced levels of the brain neurotransmitter serotonin (Coccaro, 1992; Linnoila & Virkkunen, 1992; Virkkunen, De Jong, Bartko, & Linnoila, 1989), and associations with the aforementioned temperament dimensions of impulsivity/constraint and neuroticism/negative emotionality (Krueger et al., 1996; Krueger, 1999; Verona & Patrick, 2000). These data suggest that persistent reactive aggression and impulsive suicidal tendencies may reflect expressions of externalizing vulnerability, and that low serotonin might be a biochemical marker of this vulnerability.

Intermittent explosive disorder as defined in DSM-IV (American Psychiatric Association, 1994), a syndrome marked by an inability to inhibit strong aggressive impulses, almost certainly falls within the externalizing spectrum. Certain salient features of borderline personality disorder (i.e., anger, impulsiveness, and proneness to suicide) also suggest a role of externalizing vulnerability in this disorder. The relationship of syndromes such as this to externalizing could be directly examined by including these disorders along with other known indicators of externalizing in a structural equation model.

Smoking, gambling, and compulsive sex. Evidence also exists for relations between the EXT construct and other forms of addictive behavior. Data from the MTFSS research project indicate that paternal history of drinking is associated with heightened incidence of nicotine dependence, along with other externalizing problems, in offspring (Iacono, Carlson, Malone, & McGue, 2002). In this study, nicotine dependence, like other forms of externalizing, was associated with reduced P300 brain potential amplitude. There is also evidence that problem gambling reflects externalizing vulnerability. Slutske et al. (2001) reported that pathological gambling showed substantial associations with conduct disorder and adult antisocial behavior in a large community twin sample, and these associations were attributable mainly to genetic influences. The authors concluded that the systematic co-morbidity between gambling and antisocial behavior disorders reflects the presence of a common genetic vulnerability.

There are also indications in the literature that some forms of sexual deviance may intersect with externalizing problems. For example, recent research on a syndrome termed “compulsive sexual behavior” (CSB; Coleman, 1991; Kafka, 1997), involving excessive pursuit of sexual gratification through casual relations with others and erotic media (e.g., pornography, telephone- and cyber-sex), reveals that individuals meeting criteria for this syndrome frequently show comorbid substance abuse problems, in addition to mood disorders (Black, Kehrberg, Flumerfelt, & Schlosser, 1997; Kafka & Prentky, 1994; Raymond et al., in press). One study also reported a high prevalence of conduct disorder in the histories of individuals exhibiting CSB (Black et al., 1997).

An interesting related point is that the drug naltrexone, an opioid antagonist, has shown evidence of effectiveness in treating CSB (Grant & Kim, 2001; Raymond, Grant, Kim, & Coleman, 2002), as well as pathological gambling (e.g., Kim, Grant, & Shin, 2001), alcohol dependence (e.g., Swift, 1995), and narcotic dependence (Crabtree, 1984). Kim (1998) postulated that the effectiveness of naltrexone in treating a range of impulse-control disorders derives from its inhibitory effects on mesolimbic dopaminergic pathways, which have been viewed as the underlying substrate for the incentive salience of drug-related cues (Berridge & Robinson, 1998). This work suggests that abnormalities in the dopamine system, as well as the serotonergic system (see preceding section), contribute to externalizing vulnerability. Indeed, there is growing evidence that these neurotransmitter systems operate interdependently to regulate behavior (Miczek, Fish, deBold, & deAlmeida, 2002; Di Giovanni et al., 1999).

Psychopathy. A conceptualization that has dominated experimental research on criminal deviance is the construct of psychopathy embodied in Hare's (1991) Psychopathy Checklist-Revised (PCL-R). The PCL-R was devised to identify incarcerated offenders who exemplify Cleckley's (1976) description of the psychopathic personality. It consists of 20 items, each rated on a 0-2 scale (absent, equivocal, or present) on the basis of information obtained from a semi-structured interview and from prison files. Factor analytic studies (Harpur, Hakstian, & Hare, 1988; Hare, Harpur, Hakstian, Forth, Hart, & Newman, 1990) have revealed two correlated dimensions underlying the items of the PCL-R: Factor 1 is marked by items reflecting the emotional and interpersonal features of psychopathy (charm, grandiosity, and deceitfulness; absence of remorse, empathy, and emotional depth). Factor 2 is marked by items describing a chronic antisocial lifestyle, including child behavior problems, impulsiveness, irresponsibility, and absence of long-term goals. More recently, Cooke and Michie (2001) proposed a division of Factor 1 into two sub-dimensions: "arrogant and deceitful personality style", marked by charm, grandiosity, deceitfulness, and manipulation, and "deficient affective experience", encompassing absence of remorse or empathy, shallow affect, and failure to accept responsibility.

The affective-interpersonal symptoms encompassed by PCL-R Factor 1 have been a particular focus of interest in the psychopathy literature because Cleckley (1976) described these as most fundamental to the syndrome. For example, research has demonstrated that PCL-R defined psychopaths fail to show normal augmentation of the defensive startle reflex when exposed to stimuli that are aversive or threatening (Patrick, Bradley, & Lang, 1993; Levenston, Patrick, Bradley, & Lang, 2000), and this deficit is connected specifically to the Factor 1 component of the PCL-R (Patrick et al., 1993; Patrick, 1994; Vanman, Mejia, Dawson, Schell, & Raine, in press). The implication is that the core affective-interpersonal features of psychopathy reflect a heightened threshold for the activation of the defensive (fear) system (Levenston et al., 2000; Patrick, 1994, in press). On the other hand, PCL-R Factor 2 is interesting in light of its relations with a range of socially consequential behaviors. Child and adult symptoms of DSM antisocial personality are related selectively to Factor 2 of the PCL-R (Hare, 1991; Verona et al., 2001). Smith and Newman (1990) reported that this facet of criminal psychopathy was predictive of alcohol and drug dependence, whereas Factor 1 of the PCL-R was not (see also Reardon, Lang, & Patrick, 2002). Research has also demonstrated selective relations between PCL-R Factor 2 and various indices of reactive aggression (including child and adult fights, assault charges, and partner abuse; Patrick, Zempolich, & Levenston, 1997; Patrick & Zempolich, 1998; see also Woodworth & Porter, 2002) and suicidal behavior (Verona et al., 2001).

On the basis of its selective relations with child and adult antisocial behavior and substance dependence, we hypothesized that Factor 2 of the PCL-R reflects the broad externalizing vulnerability factor. To directly evaluate this hypothesis, Patrick, Hicks, Krueger, and Lang (2003) modeled the latent externalizing factor in a male criminal offender sample and examined its relations with the two factors of the PCL-R, modeled as latent variables using subgroups of items (“parcels”) as indicators (see Figure 2).

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Insert Figure 2 about here

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In the model, the loading for each PCL-R factor on EXT reflects its unique relation after controlling for the other PCL-R factor. The partial association between EXT and Factor 2 approached unity, whereas the partial association between EXT and Factor 1 was nonsignificant and in the negative direction. The results of this analysis indicate that one facet of psychopathy as indexed by Hare's PCL-R, the social deviance component (PCL-R Factor 2), reflects the latent vulnerability dimension that underlies the externalizing disorders within the DSM.

These findings challenge the notion that the social deviance facet of psychopathy is simply a by-product of the affective-interpersonal facet. Its unique relationship to EXT instead implies that scores on this psychopathy factor index an individual's position along a latent continuum that is substantially genetic, that reflects variations in neuro-cognitive processing, and which represents proneness toward a broad range of acting-out and addictive behaviors. In this regard, Patrick and Lang (1999) postulated that acute alcohol intoxication, which produces impairments in cognitive-attentional processing and behavioral inhibition, might provide a model of neuro-cognitive deficits underlying PCL-R Factor 2 (see final section below). On the other hand, the absence of a relationship between PCL-R Factor 1 and EXT suggests that these features of psychopathy reflect a distinct etiologic mechanism (i.e., deficient emotional reactivity). This interpretation is in turn consistent with evidence for unique psychophysiological and psychometric correlates of this PCL-R factor

#### P300 as a Marker of the Externalizing Vulnerability Dimension.

Prior research studies have yielded clues as to the nature of psychobiological factors that might underlie the EXT vulnerability dimension. One relevant body of work consists of investigations of empirical, psychophysiological markers of disorders within this spectrum. For example, compelling evidence exists for abnormalities in brain potential response among individuals who have alcohol problems or who are at risk of such by virtue of a family history of alcoholism (Begleiter, Porjesz, Bihari, & Kissin,

1984). The most reliable finding in studies of at-risk individuals is that they show a reduction in the amplitude of the P300 component of the ERP in visual processing tasks (with some evidence also for auditory tasks; Polich, Pollock, & Bloom, 1994). The P300 is a positive scalp potential, maximum at parietal sites, that follows the occurrence of infrequent, attended targets in a stimulus sequence. [The term P3b is sometimes used for this frequency-sensitive component, to distinguish it from the “P3a” or “novelty P3”, maximal at fronto-central sites, that follows the occurrence of an unexpected rare nontarget stimulus; Coles & Rugg, 1995.] The most widely accepted theory of the P300 is that it reflects the updating of information in working memory (Donchin, 1981; Donchin & Coles, 1988). Thus, a reduction in P3 amplitude implies a difference in higher level cognitive functioning in individuals at risk for alcohol dependence. Another example of a psychophysiological risk indicator is resting heart rate (HR), which has been shown to be reliably lower among adults exhibiting antisocial deviance and children manifesting antisocial behavior problems later in life (Raine, 1993).

A limitation of this existing work is that it has focused on individual syndromes, such as alcohol abuse and antisocial deviance. Consequently, from the perspective of the hierarchical model articulated above, it is unclear whether indicators such as P300 amplitude and resting HR constitute markers of the broad vulnerability factor that is common to the EXT disorders, or of particular disorders within this spectrum (i.e., specific facets of EXT). In the case of P300 amplitude, there are grounds for thinking this variable may reflect the broad EXT dimension rather than just the specific alcohol dependence facet. Evidence of reduced P300 has been reported for other disorders within this spectrum (e.g., Bauer, O’Connor, & Hesselbrock, 1994; Johnstone & Barry, 1996; Klorman, 1991), and findings from the MTFs project, which assessed P300 brain response as well as symptoms of various externalizing disorders in twin participants and their family members, strongly reinforce this picture: Within the 17-year-old cohort of this study, male participants meeting DSM criteria for ADHD, conduct disorder (CD), oppositional defiant disorder (ODD), nicotine dependence, alcohol abuse or dependence, and drug abuse or dependence all showed reduced P3 in comparison to controls (Iacono

et al., 1999; Iacono et al., 2001, 2002). Moreover, unaffected individuals at risk for such disorders by virtue of a paternal diagnosis of alcoholism, drug abuse/dependence, conduct disorder, or adult antisocial behavior also showed reduced P300 amplitude (Carlson, Katsanis, Iacono, & Mertz, 1999; Iacono et al., 2002).

Recently, we used data from the MTFSS to directly examine P300 as a marker of the EXT vulnerability factor (Patrick, Bernat, Malone, Krueger, McGue, and Iacono, 2003). We hypothesized that P300 amplitude would be negatively associated with scores on the broad EXT dimension, and that this association would account for the link between P3 and individual disorders within the externalizing spectrum. This study also formally evaluated reduced P300 as a marker of externalizing vulnerability by performing a factor analysis with P300 amplitude included along with disorder symptom scores as variates. If P300 amplitude is a marker of externalizing vulnerability, we predicted that it would load significantly with the symptom variables on a single common factor rather than defining a separate factor unto itself. However, because P300 is assessed in a distinct measurement domain (i.e., physiological reactivity), we expected the magnitude of its relations with externalizing vulnerability to be lower than relations for the diagnostic indicators (cf. Campbell & Fiske, 1959).

The study sample consisted of 346 adolescent males from the MTFSS community twin sample assessed diagnostically and physiologically at the age of 17. Scores on the externalizing vulnerability factor were derived from a principal components analysis of symptom counts for conduct disorder, adult antisocial behavior, alcohol dependence, and drug dependence. Loadings of the individual symptom variables on this externalizing vulnerability (EXT) factor were all robust and comparable in magnitude to those observed by Krueger et al. (2002): conduct disorder—.74, adult antisocial behavior—.83, alcohol dependence—.77, drug dependence—.68. Scores on this vulnerability factor were computed for each participant using the regression method, and these scores served as the externalizing variable in analyses of brain response.

P300 event-related potential response was assessed in a visual-motor task—a variant of the rotated heads “oddball” procedure used in studies of ERP responding in individuals at risk for alcoholism (e.g., Begleiter et al., 1984), involving “easy” and “difficult” conditions (see Figure 3). The task included a total of

240 trials, with each stimulus presented for 98 ms, and a mean interstimulus interval of 1.5 s (i.e., total task time = approximately 7 min). The frequent nontarget stimuli (2/3 of trials) were simple oval line drawings. The infrequent target stimuli (each 1/6 of trials) were oval drawings representing heads, on which a nose and ear were drawn in four different positions: nose either up or down, and ear on either right or left. Participants pressed a key in the right or left hand to indicate the side of the head on which the ear appeared. In the easy condition, the nose was up and thus the position of the ear in the display corresponded directly to its position with respect to the head; in the difficult position, the nose was down and thus the head had to be mentally rotated to ascertain the ear's position. The ERP, reflecting the average change in scalp potential following stimuli of each type (easy, difficult, nontarget), was recorded at left (P3), central (PZ), and right parietal (P4) electrode sites. The P300 was defined as the point between 280 and 600 ms at which amplitude of the average waveform was maximal. Amplitude scores were obtained for the two target conditions (easy discrimination, hard discrimination) and for the frequent non-target condition.

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We found no significant effect of EXT on either target response accuracy or latency, indicating that individuals low and high on the EXT factor performed similarly on the task. Three types of analyses were performed on the brain potential data. The first was a mixed-model multivariate analysis of variance (MANOVA) in which continuous scores on the EXT factor were included as the between subjects factor, stimulus condition and electrode location (Pz, P3, and P4) were included as within-subject factors, and P300 amplitude was the dependent variable. In one MANOVA, the stimulus condition factor comprised the two levels of target difficulty (easy, hard). This analysis revealed a highly significant main effect of EXT,  $F(1, 344) = 10.22, p < .005$ , with higher externalizing associated with smaller P300 responses to target stimuli. Figure 4 illustrates this by showing average ERP response to target stimuli for participants in the lowest and highest

thirds of the score distribution on the EXT factor. In a second MANOVA, target conditions were aggregated and the stimulus factor instead consisted of target (heads) versus non-target (oval) stimuli. This analysis also revealed a main effect of EXT,  $F(1, 344) = 14.48, p < .001$ , and no interaction with stimulus type, indicating that individuals higher in externalizing showed reduced P300 response to both target and non-target stimuli.

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A second type of analysis was conducted to evaluate the hypothesis that scores on the EXT vulnerability factor would account for relations between P300 and individual disorders, including alcohol dependence. To test this hypothesis, we performed hierarchical regression analyses separately for each DSM disorder, with the symptom count for that disorder entered as the sole predictor of P300 amplitude in the first step, and EXT score added in the second step. For all disorders (conduct disorder, adult antisocial behavior, alcohol dependence, drug dependence), a significant relation with P300 amplitude was found in the first step, with raw regression coefficients (Bs) ranging from  $-.83$  to  $-1.22$ , all  $ps < .05$ . However, with the entry of EXT in the second step, all associations between disorder symptoms and P300 amplitude were reduced to nonsignificance, with Bs ranging from  $-.59$  to  $.32$ , all  $ps > .29$ .

Finally, to formally evaluate P300 amplitude as a marker of externalizing and to quantify its relation with the EXT factor, we conducted a principal components analysis in which overall P300 amplitude score (across all stimuli and electrode sites) was included as a variate together with symptom scores for the four disorders. A single dominant component emerged from this analysis, accounting for 49.7% of the total variance in scores. The eigenvalue for this component was 2.49, with all other eigenvalues less than one. Loadings for the four symptom variables on this component were substantial: CD—.75; AAB—.83; AD—.81; and DD—.69. The loading for P300 amplitude was more modest ( $-.32$ ), presumably owing to unique method variance associated with physiological measurement versus interview-based symptom assessment (cf.

Campbell & Fiske, 1959). However, this loading was nevertheless highly significant,  $p < .01$ . The fact that P300 amplitude loaded with the symptom variables on a common factor rather than defining a separate method component indicates that it is tapping the same underlying construct as the symptom variables.

These findings indicate that P300 is a marker of the common vulnerability that underlies antisocial syndromes and substance use disorders, rather than a marker of alcohol problems per se. Individuals higher on the externalizing dimension showed reduced P300 amplitude for non-target stimuli as well as targets. This implies a general difference in the evaluative processing of stimuli rather than a specific impairment in context updating associated with target identification (Donchin, 1981; Donchin et al., 1986). However, higher externalizing was not associated with poorer task performance as indexed by accuracy of discrimination or response time. This argues against a lack of engagement or uncooperativeness as an explanation for reduced P300 amplitude.

The fact that P300 response amplitude, like externalizing vulnerability, is highly heritable (Katsanis et al., 1997; O'Connor et al., 1994) raises the possibility that P300 amplitude may represent a quantitative endophenotype of externalizing vulnerability. An endophenotype is a biological characteristic that arises from, and thus directly reflects, an underlying genotypic predisposition (Gottesman & Shields, 1972; Iacono, 1998; John & Lewis, 1966). If reduced P300 is an endophenotype for externalizing vulnerability, it should also occur at higher rates among asymptomatic individuals who are at risk for developing externalizing problems by virtue of a positive parental history of such problems (cf. Elmasian et al., 1982).

Consistent with this, Iacono et al. (2002) reported reduced P300 in the adolescent sons of fathers who met criteria for alcohol dependence, drug abuse/dependence, or antisocial personality, whether or not the offspring themselves met criteria for a diagnosis. These investigators also found that reduced P300 at age 17 predicted the development of externalizing problems of various kinds at age 20, even among individuals who were free from disorder at the time of P300 assessment. From these findings, it seems reasonable to expect that higher levels of externalizing vulnerability in fathers would predict smaller P300

amplitude in their offspring, and that individuals with reduced P300 amplitude early in life would show higher levels of externalizing symptomatology later in life. Findings in support of these hypotheses would have important practical implications: They would indicate that P300 amplitude can be used, in combination with other risk indicators (cf. Iacono et al., 2000), to identify vulnerable individuals early in life, at a time when preventative strategies are likely to be most effective.

A further point concerns the relevance of these findings to the literature on psychopathy and brain response. As noted above, there is a close relation between the construct of externalizing and the antisocial deviance component (Factor 2) of Hare's PCL-R (Patrick et al., 2003a). From this relation, one might expect to find reduced P300 amplitude among individuals diagnosed as psychopathic. However, findings of studies on psychopathy and P300 response have been mixed—with some studies showing enhanced rather than reduced P300 amplitude in individuals diagnosed as psychopathic (cf. Raine, 1989). One possible reason is that these studies have employed widely varying task procedures, some markedly different from the standard “oddball” paradigm. Moreover, the two PCL-R factors have not been considered separately in analyses. The strongest prediction is of a relation between reduced P300 and the antisocial deviance factor of psychopathy. It may be that reliance on total psychopathy scores obscures this relation. A parallel is evident in the literature on neuropsychological test performance in psychopathic and antisocial individuals: Whereas individuals defined as psychopathic on the basis of overall scores on Hare's checklist appear not to differ on standardized indices of frontal lobe function (Hare, 1984; Hart, Forth, & Hare, 1990), a meta-analysis by Morgan & Lilienfeld (2000) revealed clear evidence of differences among individuals defined more broadly as antisocial. A final factor could be that participants in psychopathy studies are generally older than individuals in community high-risk studies. There are some data indicating stronger associations between risk status and P300 amplitude in younger versus older individuals.

### Brain Substrates of Externalizing Vulnerability

The finding of a relation between reduced P300 amplitude and externalizing vulnerability is important because it suggests a basis for prospectively identifying individuals at risk for varying problem behaviors within this spectrum. However, the implications of this connection for a functional understanding of the neurobiology of externalizing vulnerability remain unclear. Begleiter & Porjesz (1999) postulated that the inherited predisposition to alcohol dependence entails a hyperexcitability of the central nervous system that enhances risk for a variety of disinhibitory syndromes. In this model, reduced P300 amplitude is thought to reflect a diminished capacity for neuronal inhibition. Relatedly, Iacono et al. (2000) proposed that vulnerability to substance abuse and antisocial deviance reflects a dysfunction in inhibitory control associated with frontal brain regions (see also Giancola & Tarter, 1997), and that reduced P300 response is one indicator of this inhibitory deficit.

However, the issue of what psychological process(es) are indexed by the P300 is an ongoing topic of debate (REFS), and the latest research on the underlying sources of the P300 potential indicate that it is diffusely generated rather than indicative of activity within a distinct brain region (REFS). Therefore, to gain a more precise understanding of the neuro-cognitive basis of the externalizing vulnerability, it will be necessary to employ task procedures that are known to index activity in specific brain regions. Several lines of evidence point to frontal brain regions as a key focus of investigation.

First, there is extensive evidence supporting the role of the prefrontal cortex in “executive functions” such as response inhibition, planning, and verbal mediation of behavior (Fuster, 1980; Stuss & Benson, 1986; Tranel & Damasio, 2000). Second, lesions of frontal brain areas are known to result in impulsive, externalizing behavior (Blumer & Benson, 1975; Damasio, Tranel, & Damasio, 1990). Third, deficits on neuropsychological tests of frontal lobe function have been reliably demonstrated for a number of the externalizing syndromes. In this regard, Morgan and Lilienfeld (2000) reported compelling meta-analytic evidence for deficits on such tasks in individuals exhibiting conduct disorder and adult antisocial

behavior. Barkley (1997) proposed on the basis of a review of neuropsychological studies that frontal brain dysfunction characterizes the most prevalent form of ADHD, the hyperactive-impulsive type. Individuals at risk for alcoholism by virtue of a positive parental history also show evidence of impairment on neuropsychological tests of frontal lobe function (Peterson & Pihl, 1990; Tarter, Alterman, & Edwards, 1985).

A limitation of this existing work is that the traditional neuropsychological tests used in these studies (e.g., Wisconsin Card Sorting Task; Porteus Maze Task; Trailmaking Task) do not differentiate impairments associated with anatomically distinct frontal regions (cf. Lezak, 1995). In this regard, an important distinction concerns dorsal versus ventral subdivisions of the prefrontal cortex (PFC), believed to be differentially involved in cognitive versus motivational facets of executive functioning, respectively (Robbins, 1998; Rosenkilde, 1979). The dorsolateral PFC has been shown to play a critical role in working memory processes, involving the maintenance of a discrete stimulus representation across a temporal delay (Goldman-Rakic, 1996). In humans, performance of a working memory task that involves matching current stimuli to earlier stimuli in an ongoing stream (the “n-back” task; Cohen et al., 1994) preferentially activates the dorsolateral PFC, with the degree of activation increasing as a function of memory load (Cohen, Perlstein, Braver, Nystrom, Noll, Jonides & Smith, 1997). Additionally, this region of the PFC is believed to be involved in more active processes associated with inhibition and regulation of behavioral responses (Petrides, 2000). Thus, the dorsolateral PFC is also selectively involved in performance of the visual antisaccade task, which entails active inhibition and re-direction of reflexive eye movements (Broerse, Crawford, & den Boer, 2001; Muri et al., 1998).

On the other hand, ventromedial and orbitofrontal regions of the PFC (collectively termed orbitomedial PFC; e.g., Blumer & Benson, 1975) play more dominant roles in the anticipation of affective consequences of behavior (Bechara, Damasio, Tranel, & Damasio, 1997) and in the unlearning of stimulus-reward associations (i.e., reversal learning; Dias, Robbins, & Roberts, 1996; Rolls, 2000). As an

illustration of the anatomic specificity of different neuro-cognitive tasks, Bechara, Damasio, Tranel, and Anderson (1998) reported that patients with dorsolateral PFC lesions showed impairments on a working memory tasks but not on a “gambling” task involving affect-guided decision-making, whereas the reverse was true of patients with ventromedial PFC lesions.

Recently, Miller and Cohen (2001) proposed an integrative model of PFC function, highlighting its integral contribution to regulative cognitive control. According to this model, the control functions of the PFC arise from its specialized capacity for on-line maintenance of goal representations: By maintaining patterns of activation corresponding to goals and methods to achieve them, the PFC provides biasing signals to other regions of the brain with which it connects. These signals serve to prime sensory-attentional, associative, and motor processes that support the performance of a designated task, by directing activity along relevant brain pathways. An appealing feature of this model is that it provides a mechanistic account of PFC function that avoids the circularity of mentalistic (i.e., PFC as “executive”) accounts.

Miller and Cohen’s model focuses predominantly on regulative cognitive control functions associated with the dorsolateral PFC. This division of the PFC has been studied most extensively in relation to schizophrenia, but some indirect evidence exists to suggest a role of the dorsolateral PFC in externalizing psychopathology. For example, the antisaccade task was administered as part of the MTFIS project protocol. Behavior genetic analyses of data for a subset of 17-year-old female twin participants indicates that error rates on this task are substantially heritable (coefficient = .6; Malone et al., 2001), and preliminary analyses of error rates as a function of diagnostic risk status revealed significantly elevated rates in high-risk boys with a paternal history of both substance abuse/dependence and antisocial personality disorder in comparison to paternal-history-negative boys (Iacono, 1998; see also Iacono, Carlson, & Malone, 2000). Furthermore, error rates were elevated similarly in paternal-history-positive boys with and without a personal substance abuse history, indicating that diminished antisaccade

performance reflected genetic liability rather than the presence of a substance diagnosis per se. In other research described in the next section below, we have found evidence that alcohol impairs inhibitory control under high-load conditions in the n-back working memory task (Casbon, Curtin, Lang, & Patrick, in press). Taken together, these findings indicate that the role of the dorsal PFC in actively moderating prepotent responses is compromised in disinhibitory syndromes and states.

Miller and Cohen (2001) posited that the ventral subdivision of the PFC, which has close connections with limbic structures, may be especially important for regulating emotional reactivity and expression. Insofar as externalizing problems involve impairments in control of negative affect (e.g., anger and aggression) and appetitive drives, it is reasonable to suppose that impairments in orbitomedial PFC function contribute to externalizing problems. Experimental evidence of deficient emotion regulation in externalizing individuals comes from a task called the “cooltest” procedure, which was included in the MTFs protocol. This procedure involves measurement of electrodermal reactivity to signaled and unsignaled noise blasts. Predictability of the blasts was associated with attenuated phasic response among participants who were asymptomatic for alcohol or drug dependence, but not among participants manifesting substance problems (Iacono, 1998; see also Finn, Kessler, & Hussong, 1994). The implication is that substance abusers were less able to regulate their emotional reactions to the stressor as a function of the warning signal—a finding reminiscent of the failure of patients with ventromedial PFC lesions to anticipate aversive consequences of faulty decisions (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara et al., 1997). Diminished responsivity in anticipation of punishment is also characteristic of antisocial (Raine, 1993) and psychopathic individuals (cf. Hare, 1978; Siddle & Trasler, 1981), suggesting a link to the broader externalizing construct.

Another anterior brain region with potential relevance to externalizing psychopathology is the anterior cingulate cortex (ACC), which is viewed as playing a central role in action monitoring (Bush, Luu, & Posner, 2000; Luu, Flaisch, & Tucker, 2000) or evaluative control (Botvinick et al., 2001). Recent research suggests subdivisions of the ACC paralleling those for the PFC (i.e., dorsal-cognitive and ventral-

affective subdivisions; Bush et al., 2000). The role of the ACC has been examined particularly in relation to errors on speeded reaction time tasks (cf. Gehring, Himle, & Nisenson, 2000). One variable of interest in such studies is the error-related negativity (ERN), a negative-polarity scalp potential that peaks within approximately 100 ms following an incorrect reaction time response. The ERN is theorized to reflect an error detection (Scheffers et al., 1996) or conflict monitoring process (Carter et al., 1998), and brain source localization studies have converged on the ACC as its probable generator (Miltner, Braun, & Coles, 1997; Holroyd, Dien, & Coles, 1998; Luu et al., 2000). Dikman and Allen (2000) reported that individuals low on a measure of socialization, a construct related to EXT, showed reduced ERN response in a speeded reaction time paradigm. Other work, reviewed below, indicates that the magnitude of the ERN is reduced during alcohol intoxication. In contrast, individuals with obsessive compulsive disorder, who conceptually are at the low pole of the inhibition-disinhibition (EXT) continuum (Gray, 1982), show enhanced ERN (Gehring et al., 2000).

To summarize, the available data indicate that deviations in frontal brain function contribute to externalizing psychopathology. However, research to date has focused on individual diagnostic syndromes using assessment procedures that are not equipped to index the functioning of specific subdivisions of the PFC. We argue, from the standpoint of the hierarchical spectrum model, that the broad externalizing factor should be a primary target in investigations of the role of frontal brain impairments in disinhibitory syndromes. Furthermore, we encourage the use of contemporary human neuroscience paradigms, designed to index specific neuro-cognitive processes associated with specific brain regions, in this endeavor. In particular, existing data indicate that impairments in brain systems that mediate inhibition of prepotent responses and adaptive responding under conditions of response conflict are likely to be associated with externalizing vulnerability (cf. Gorenstein & Newman, 1980; Newman & Patterson, 1993). Pharmacologic manipulations that disrupt normal cognitive-affective control processes can serve as a useful experimental model in this regard. In the final section below, we summarize recent studies that

have used acute alcohol intoxication to investigate functional impairments associated with disinhibited behavior.

#### Acute Alcohol Intoxication as a Model of Externalizing Vulnerability

Alcohol is a quintessential disinhibitory drug (Gray & McNaughton, 2000). The state of intoxication is reliably associated with impulsive, risk-taking behavior and a bias toward satisfying immediate urges that would normally be inhibited. For example, acute alcohol intoxication has been observed to lead to both aggression (Bushman & Cooper, 1990) and sexual and other risk taking behaviors (Burian, Liguori, & Robinson, 2002; Morris & Albery, 2001). Moreover, intoxicated individuals display behavioral deficits in experimental paradigms requiring response inhibition such as the Go-Stop (Mulvihill, Skilling, & Vogel-Sprott, 1997), Go/No-Go (Finn, Justus, Mazas, & Steinmetz, 1999) and Stroop tasks (Curtin & Fairchild, 2003). Thus, it appears that alcohol challenge may produce acute behavioral regulation problems that match more dispositional behavior patterns displayed by high externalizing individuals (Patrick & Lang, 1999; Patrick, in press).

Recent research and theorizing on the mechanisms responsible for alcohol challenge effects on behavior has focused on the idea that alcohol disrupts cognitive control functions instantiated in anterior brain regions that are involved in inhibiting prepotent responses and mediating between competing behavioral inclinations. Given the similarities in the observed behavior patterns and purported cognitive deficits observed acutely during states of intoxication and more chronically among externalizing individuals, laboratory research involving alcohol challenge may serve to advance our understanding about neuro-cognitive mechanisms responsible for disinhibitory actions among externalizers. Specifically, alcohol challenge may prove to be a useful tool that allows experimental psychopathologists to systematically manipulate anterior neuro-cognitive function in humans to examine its potentially causal role in externalizing behavior. In addition, recent alcohol challenge work calls attention to important

methodological advances cognitive neuroscience paradigms and brain electrophysiology that can be readily utilized in clinical research on externalizing. This work is now reviewed with these goals in mind.

In an initial study examining the neurocognitive mechanisms underlying dysregulated behavior produced by alcohol challenge, Casbon, Curtin, Lang, & Patrick (2003) utilized a variant of the n-back task, a previously validated working memory paradigm (Cohen et al., 1994, 1997). In this task, a series of letter stimuli are presented sequentially and participants are required to respond with a button press if the current letter's identity matches the letter presented "n" (n=1 or 2 depending on task instructions) stimuli previous. Working memory load (light vs. heavy) was manipulated across 1- and 2-back conditions, with the 2-back condition placing substantially larger load on working memory function and the neural structures that support this component of executive function (e.g., dorsolateral PFC; Jonides, Schumacher, Smith, & Lauber, 1997). Contingencies for the task were also arranged so that an active response was required to 80% of stimuli in designated trial blocks at each memory load, and only 20% of stimuli in other blocks. This response frequency manipulation permitted assessment of the response biasing effect of a prepotent behavioral set to either respond (80% blocks) or withhold responding (20% blocks) across trials within blocks.

In this task intoxicated individuals displayed prepotent, task-inappropriate response patterns that resulted in increased rate of errors, but only under heavy working memory load (see Figure 5). This effect was evident for both commission and omission errors. Specifically, in the 80% response frequency condition that encouraged a prepotent behavioral set to respond, alcohol significantly exacerbated the rate of commission errors, much more notably under heavy memory load (top panel, gray hatched bars). Similarly, in the 20% response frequency condition that established a prepotent behavioral set to inhibit response, alcohol produced significantly more omission errors—again, specifically under conditions of heavy memory load (bottom panel, white hatched bars). Analyses of sensitivity and response bias indices from Signal Detection Theory (SDT; Green & Swets, 1966) provided further clarification of the nature of

these deficits. SDT sensitivity analyses indicated that alcohol challenge reduced participants' ability to detect letter matches in the 2-back condition, suggesting a selective effect of alcohol on working memory function. Moreover, analysis of the SDT response bias index confirmed that alcohol intoxication interacted with memory load to increase response bias in the direction of the prepotent response established by the response frequency manipulation under heavy load.

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Insert Figure 5 about here  
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These data support the thesis that alcohol-induced behavioral dysregulation resulted from impaired regulative cognitive control. SDT analyses suggested that alcohol challenge compromised working memory function, and impaired behavioral inhibition when intoxicated was selectively observed only in conditions that required intact working memory for successful regulation of behavior (i.e., heavy load trials that required inhibition of the pre-potent behavioral response set). More broadly, integration of these alcohol challenge effects and neuro-imaging evidence that documents selective dorsolateral PFC activation during heavy memory load n-back trials further substantiates claims about the key role of prefrontal cortex the regulation and/or inhibition of contextually inappropriate prepotent responding (Miller and Cohen, 2001).

Curtin & Fairchild (2003) advanced these initial results by utilizing event related potentials (ERPs) to more directly investigate the effects of alcohol challenge on anterior cognitive control processes responsible for the regulation of behavior. Intoxicated and non-intoxicated participants performed the standard Stroop task, a well-validated response conflict paradigm that requires inhibition of prepotent responding for successful task performance. A substantial body of research has established that performance deficits on incongruent color-naming trials (i.e., the Stroop interference effect) are the result of response conflict between prepotent but incorrect activation of word meaning and task appropriate but

weaker script color response activation (see MacCleod, 1991 for a review). Moreover, research employing neuro-imaging techniques has consistently documented activation of ACC on these incongruent color-naming trials (Bench et al., 1993; Carter, Mintun, & Cohen, 1995; George et al., 1994; Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000; Pardo, Pardo, Janer, & Raichle, 1990), suggesting an important contribution of ACC to task performance on these trials.

Analysis of task performance measures in this study indicated that participants in both beverage groups displayed the typical Stroop interference effect, with increased response time and error rates on incongruent color-naming trials. However, the magnitude of this interference effect differed across beverage conditions (see Figure 6), with significant exacerbation of the behavioral deficits observed among intoxicated participants on these critical trials. Moreover, these behavioral deficits resulting from alcohol challenge were selectively exhibited on incongruent, color-naming trials. Task performance was comparable across beverage groups in all other conditions.

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As indicated above, ERPs were also collected to examine cognitive control function. Recent basic research with the Stroop task has identified two frontal ERP component correlates of anterior cognitive control processes necessary for adaptive Stroop performance, N450 and the negative slow wave (NSW). The N450 is a phasic negative deflection of the ERP waveform with a fronto-central distribution. This component appears to be sensitive to the detection of response conflict in the Stroop task (Liotti, Woldorff, Perez, & Mayberg, 2000; Rebai et al., 1997; West & Alain, 1999, 2000a, 2000b, 2000c) and an initial source localization study indicated that it may be ACC generated (Liotti et al., 2000). Thus, Curtin & Fairchild (2003) suggest that this component is an electrophysiological correlate of evaluative control/action monitoring processes in the Stroop task. The NSW is a frontal tonic negative slow wave that has been observed to covary with activation and implementation of

regulative control processes (West & Alain, 1999, 2000a, 2000c) and component topography suggests a neural generator in the polar or dorsolateral prefrontal cortex (West & Alain, 2000c). Curtin & Fairchild (2003) observed that alcohol challenge significantly attenuated both of these frontal ERP components on incongruent color naming trials. Moreover, alcohol did not alter the magnitude or latency of earlier parietally located ERPs that prior research has linked to initial detection, encoding, and evaluation of Stroop stimulus features (Duncan-Johnson & Kopell, 1981). Thus, these ERP results strongly suggest that the observed behavioral deficits on incongruent color naming trials are the result of impaired function in anterior brain regions important for inhibition of maladaptive prepotent responding when stimuli elicit competing behavioral inclinations.

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Insert Figure 7 about here  
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A recently completed study involving alcohol challenge in a variant of the Flanker paradigm provided the strongest evidence to date to support the thesis that selective anterior cognitive control function deficits are responsible for failures in prepotent response inhibition (Curtin & Green, 2003). Participants performed a choice reaction time task to target letters (H or S) surrounded by either compatible (e.g., HHHHH) or incompatible flanker letters (e.g., SSHSS) and responded on each trial with one of two buttons held in separate hands to indicate the identity of the target letter. Previous basic research with the Flanker task indicates that the manipulation of flanker compatibility primarily affects stimulus evaluation processes (Coles et al., 1995; Fournier et al., 1997). Curtin & Green (2003) also manipulated the relative probability of the two target letters such that one of the target letters (and associated button response) occurred more frequently (i.e. 80% of trials). This manipulation was designed to produce the gradual development of a dominant or prepotent response over trial blocks from repeated frequent execution of one letter stimulus-response pairing relative to the other across the experiment. Based on the research described above (Casbon et al., 2003; Curtin & Fairchild, 2003), alcohol challenge

was expected to selectively impair performance on infrequent target trials because of deficient inhibition of the incorrect but prepotent frequent target response resulting from impaired cognitive control function when intoxicated.

Two specific ERP indices (P3 & Error related negativity) were assessed to further examine potential anterior neurocognitive deficits underlying impaired prepotent response inhibition. As described earlier, P3 likely represents the summation of activity of multiple neural generators in the service of separable cognitive processes (Fabiani et al., 2000). Substantial evidence indicates that P3 is sensitive to stimulus evaluation processes (Kutas et al., 1977) with notable delay and reduction in this component observed in response to manipulations that decrease stimulus detectability or discrimination (Duncan-Johnson & Kopell, 1981; Hillyard et al., 1971). Therefore, variation in P3 resulting from the Flanker Compatibility manipulation (i.e., reduction in P3 on incompatible vs. compatible flanker trials) was utilized to index the integrity of stimulus evaluation processes in the Flanker task. However, the P3 component also covaries with the allocation of anterior cognitive control resources that support task-relevant processing (Roth et al., 1976; Donchin & Coles, 1988; Kramer & Spinks, 1991) and McCarthy et al (1997) recently confirmed that infrequent, task-relevant events that elicit increased parietal P3 also activate prefrontal cortex, a neural structure implicated in cognitive control function as reviewed above. Therefore, P3 variation in response to the Target Frequency (i.e., increased P3 to infrequent vs. frequent targets) was utilized to assess regulative cognitive control function on the critical infrequent trials that required inhibition of the prepotent frequent target response. Finally, Error Related Negativity (ERN), an electrophysiological index of action monitoring processes in response to task related errors, was also included to assess anterior evaluative control function instantiated in the ACC.

Results provided strong support for a selective behavioral effect of alcohol challenge on prepotent response inhibition. The Target Frequency manipulation resulted in the development of a prepotent response tendency that increased in strength over trial blocks due to repeated execution of the frequent

target/response mapping. In this context, intoxicated participants displayed increasing difficulty over blocks executing the relatively weaker, infrequent response as competition from developing prepotent frequent target response increased (see Figure 8). In contrast, no such behavioral deficit was observed in non-intoxicated participants. Moreover, this selectivity of this alcohol-induced impairment of prepotent response inhibition of prepotent responding highlighted by the robust responding to perceptually complex, incompatible flanker trials when intoxicated. Although all individuals displayed sizeable response slowing on incompatible flanker trials, there was no indication of an exacerbation of these stimulus evaluation difficulties among intoxicated individuals (mean slowing on incompatible trials of 58.0 vs. 57.9ms in no-alcohol and alcohol groups, respectively).

Alcohol challenge effects on ERP indices provided further evidence about candidate neurocognitive mechanisms for these inhibitory deficits. Alcohol intoxication did not affect P3 variation in response to the Flanker Compatibility manipulation. All participants displayed the expected reduction in P3 on incompatible flanker trials, but the magnitude of this reduction did not differ across beverage groups. Thus, consistent evidence of intact stimulus evaluation processes when intoxicated was obtained regardless of whether these processes were assessed peripherally via their impact on eventual behavioral response or more centrally with P3. In contrast, alcohol did significantly reduce P3 associated with cognitive control function that varied in response to the Target Frequency manipulation (see Figure 9). Intoxicated individuals displayed sizably reduced P3 on infrequent trials relative to controls, suggesting a reduction in the amount of regulative cognitive control brought to bear on these infrequent trials. Alcohol challenge also produced a significant reduction in ERN (see Figure 10) and the magnitude of this reduction significantly predicted the degree of response slowing over blocks on infrequent target trials among intoxicated participants.

Synthesis of these ERN and P3 results with previously reviewed research from our laboratory described above (Casbon et al., 2003; Curtin et al., 2003) and current theory on cognitive control

(Botvinick et al., 2001; Miller & Cohen, 2000) suggests the following about the neurocognitive mechanisms underlying failures in prepotent response inhibition when intoxicated. Alcohol may impair ongoing evaluative control processes that are instantiated in the ACC and are necessary for adaptive action monitoring (Luu et al., 2000). Although speculative, recent evidence suggests such impairment could occur through alcohol's influence on the mesencephalic dopamine system (Harris et al., 1992; Nieuwenhuis et al., 2002). As a result of deficit action monitoring, prefrontal regulative control resources that are critical to support goal-directed behavior are not adequately recruited when competing response inclinations are activated. Therefore, intoxicated individuals' behavior will be more "stimulus-driven", regardless of whether the most activated stimulus-response association is consistent with current goals. Moreover, they will be less likely to adjust performance in response to indications (task errors, response conflict) that their current behavioral course is not likely to achieve its intended goal (Ridderinkhof et al., 2003).

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In summary, our research in this area demonstrates that acute intoxication can serve as a model of how deficits in cognitive functioning can interfere with behavioral inhibition in complex or competing stimulus contexts. The broader behavioral implications of these effects of alcohol are illustrated by findings from two aggression studies reported by Zeichner and Pihl (1979; 1980). In the first of these, nonintoxicated participants modulated their behavior in response to subtle feedback indicating a "quid pro quo" relationship between the intensity of shocks that they delivered and those received from a supposed competitor. However, alcohol-intoxicated participants were insensitive to the feedback: They persisted in delivering high intensity shocks despite the adverse consequences for themselves. Parallel results were obtained in the second experiment: Unlike sober participants, intoxicated individuals did not reduce the

levels of shock they delivered to an opponent when advised that the latter had no control (versus complete control) over the shock intensities administered to the participant.

These findings underscore the impairments in reflectivity and planning associated with intoxication, and the affiliated insensitivity to threat or punishment cues. Alcohol-intoxicated individuals seemed willing to risk personal harm in order to react to the immediate situation with the most dominant and immediately gratifying response. Behavior of this kind is also typical of high externalizing individuals and may reflect parallel disturbances in cognitive-affective control.

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## Figure captions

Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5. Mean commission error rates (top panel) and omission error rates (bottom panel) by Beverage group, Memory load (light load = one-back; heavy load = two-back) and Block response frequency.

Figure 6. Stroop task accuracy (top panel) and response time (bottom panel) as a function of beverage, task and condition.

Figure 7. Average event related potential waveforms across central anterior scalp sites (Fz and FCz) for the Stroop color-naming task by beverage and condition. Stimulus onset is at 0 ms. N450 magnitude was scored within the 100 ms window (indicated with left box) from 400 – 500ms post stimulus onset. The negative slow wave was scored within the 500 ms window (indicated with right box) from 1000 ms to the end of the epoch.

Figure 8. Flanker task response time on infrequent trials as a function of beverage and block. B1=Block 1, B2=Block2, B3=Block 3, B4=Block4. Error bars are standard error of mean.

Figure 9. Event related potential waveforms at the Pz scalp site by beverage and target frequency. Stimulus onset is at 0 ms. P3 was scored within the 200ms window between 306 – 506ms post stimulus onset (200 ms window surrounding grand average waveform peak response).

Figure 10. Event related potential waveforms for error trials at the Cz scalp site by beverage. Participant response is at 0 ms. Error related negativity (ERN) was scored as the between 0 – 100ms post response.

Figure 5

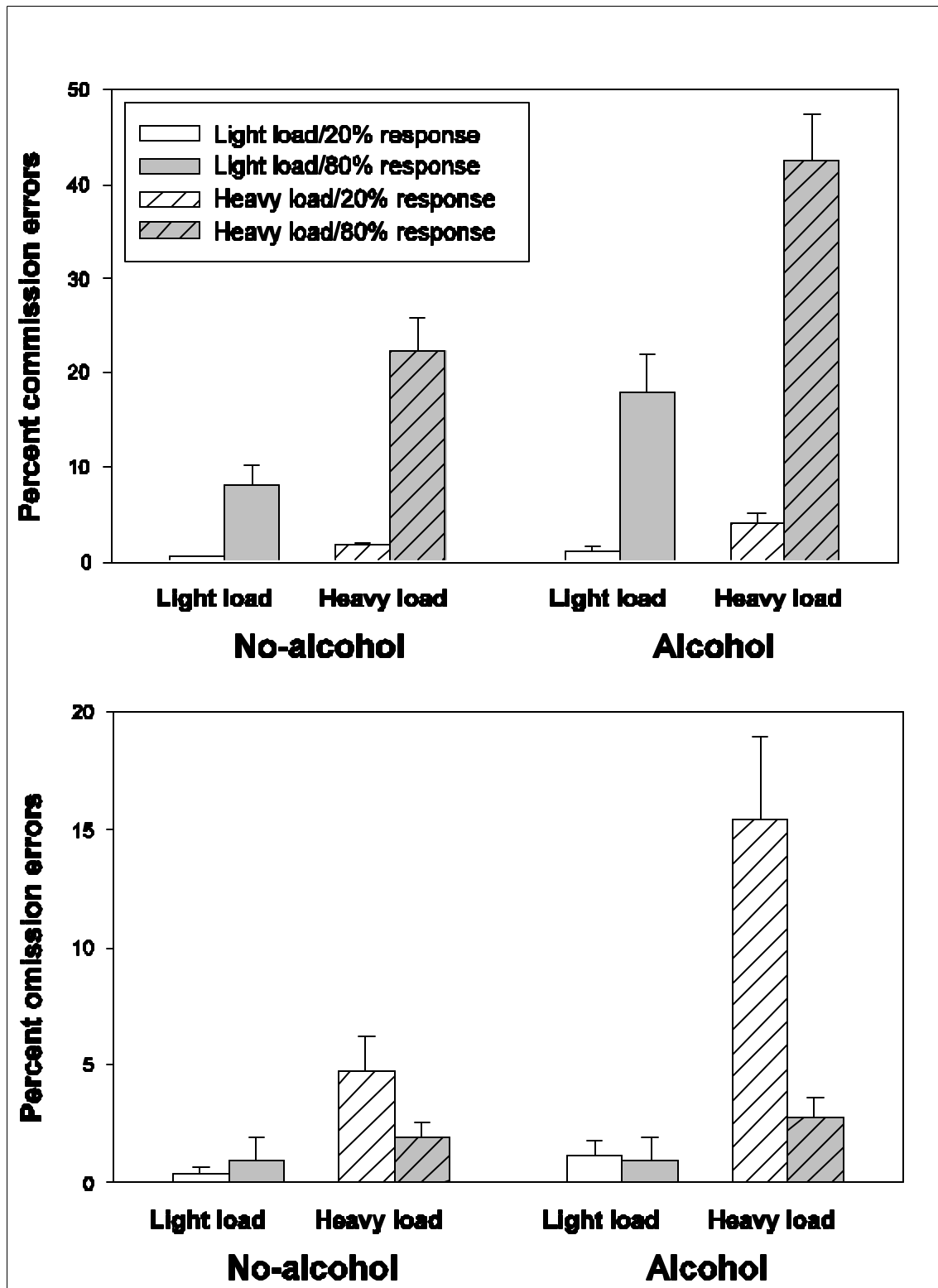


Figure 6

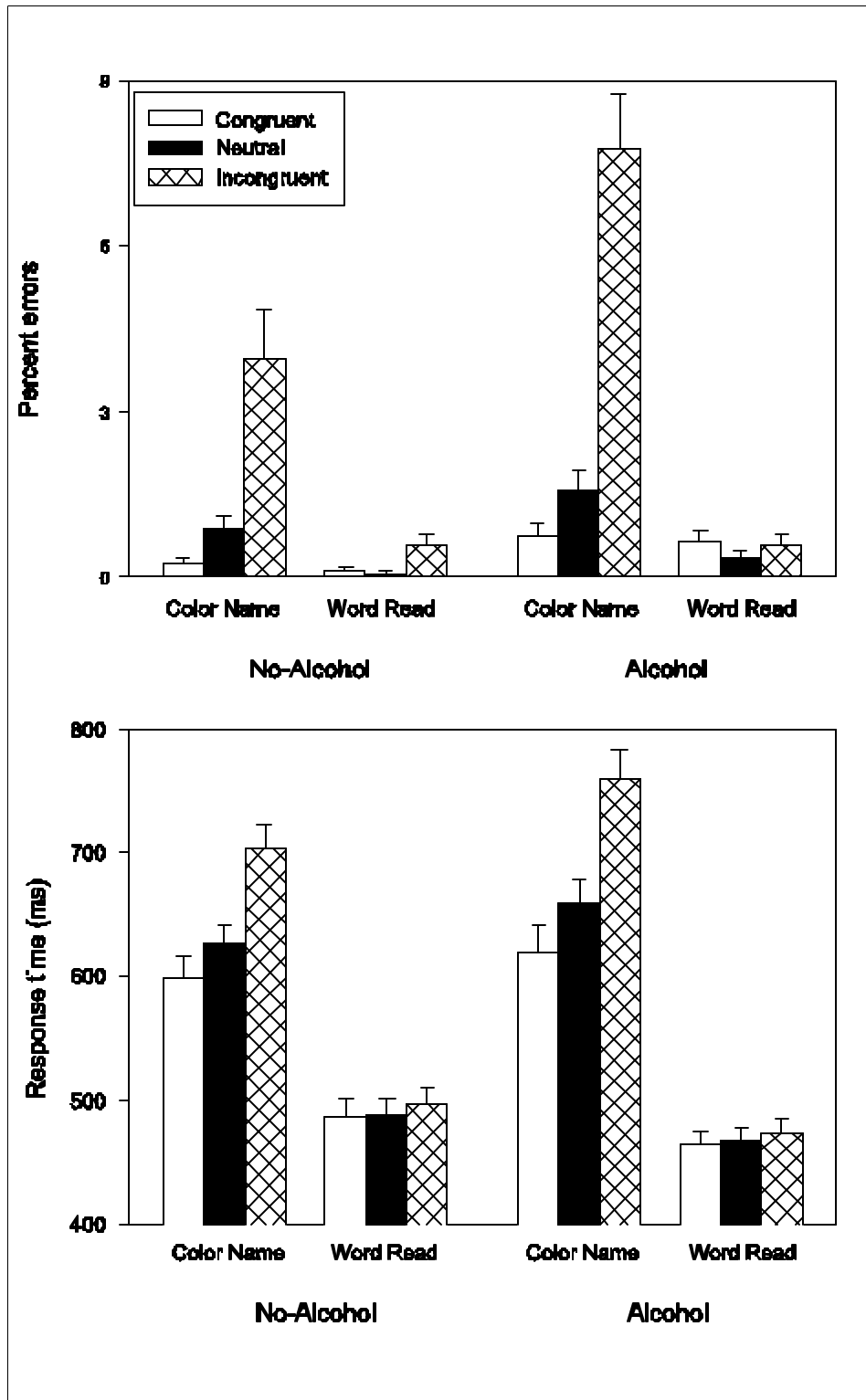


Figure 7

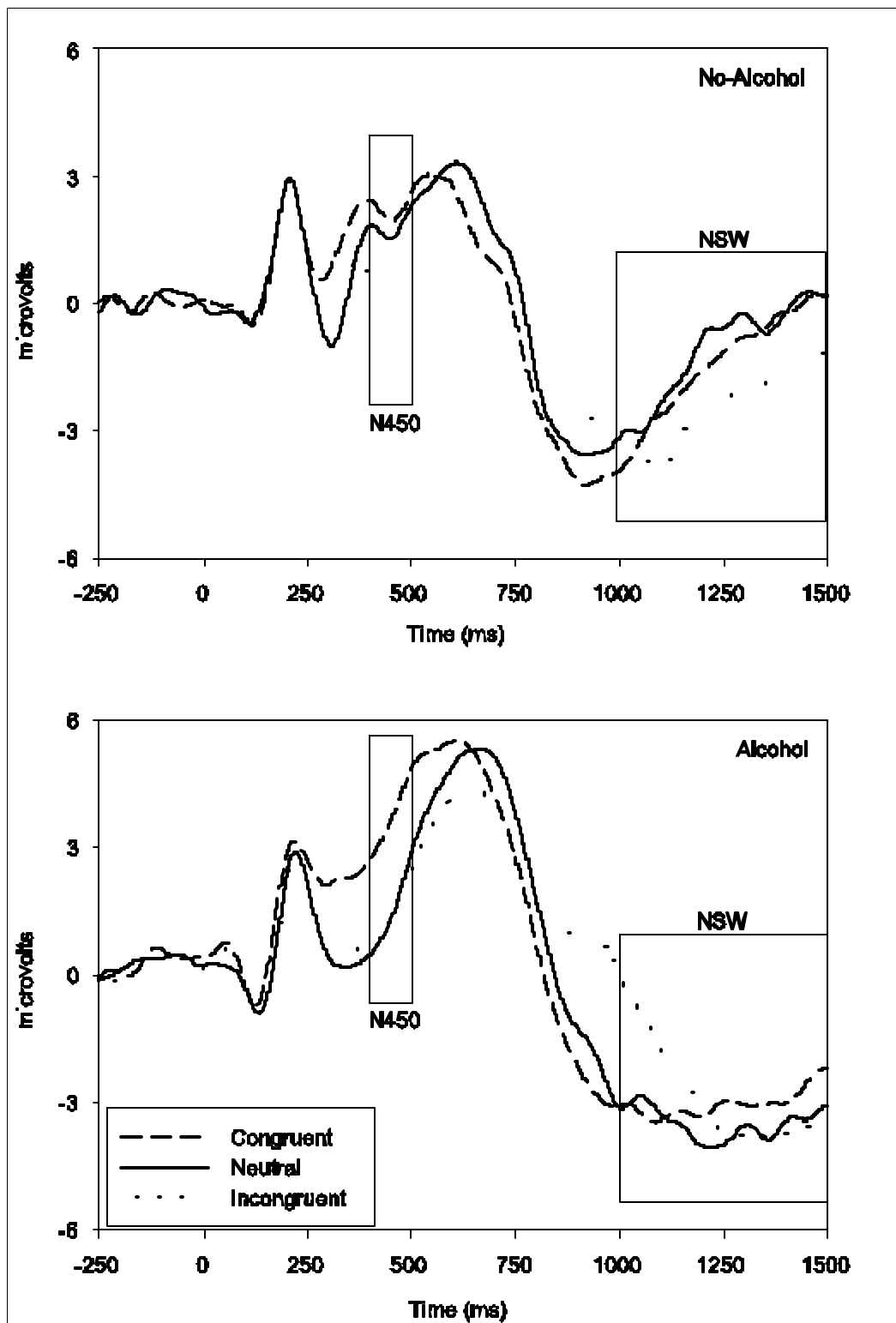


Figure 8

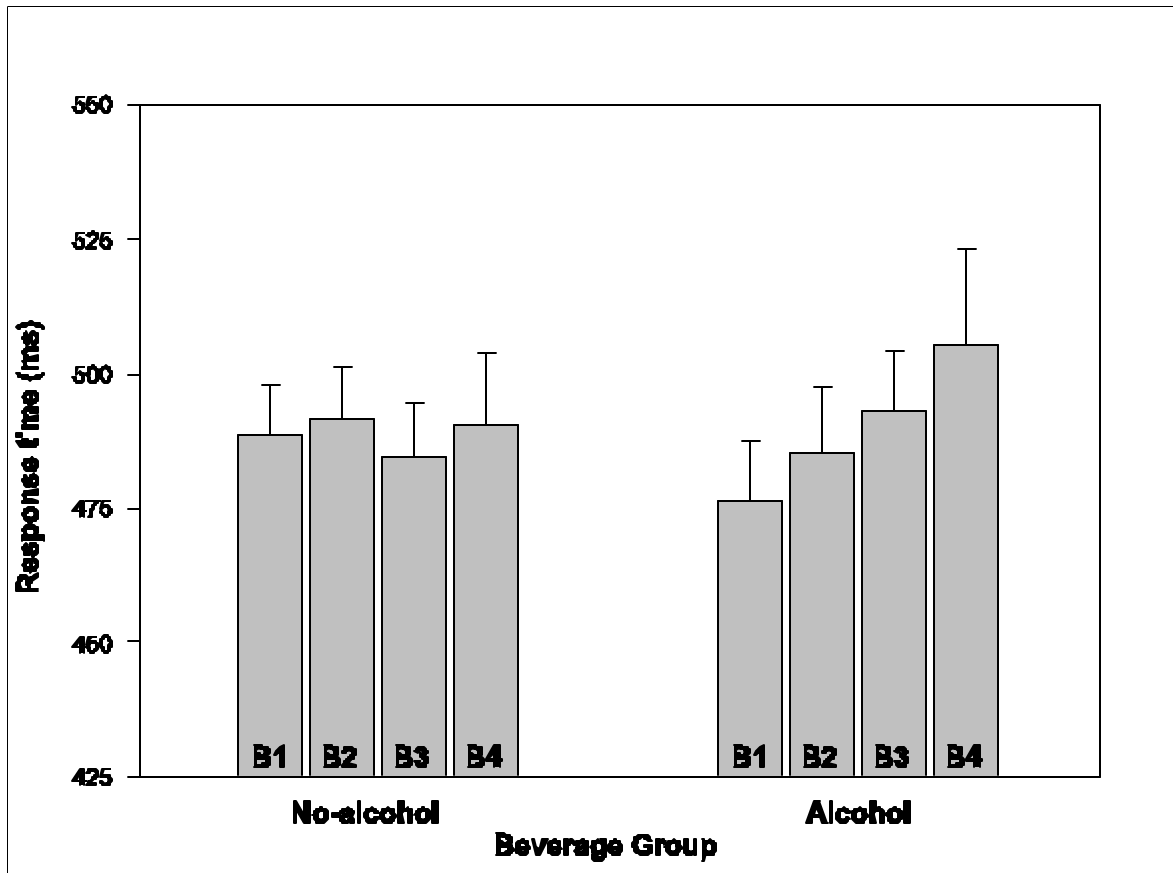


Figure 9

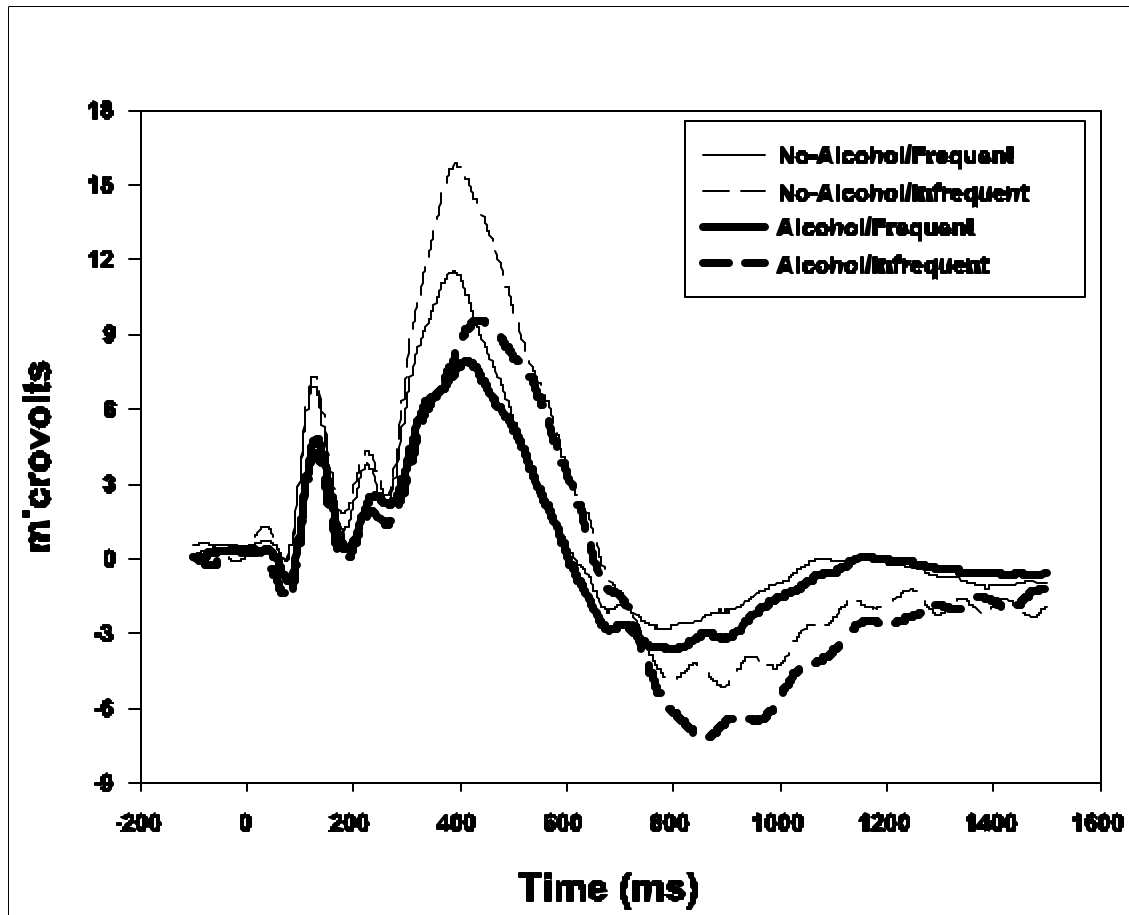


Figure 10

