Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude

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Abstract

We hypothesize the existence of an inherited predisposition for a spectrum of behaviors and traits characterized by behavioral disinhibition. This externalizing spectrum includes childhood disruptive disorders, antisocial behavior, substance use disorders, personality traits related to behavioral undercontrol, and the precocious expression of problem behavior. We further hypothesize that a genetically influenced central nervous system diathesis underlies this spectrum and is reflected in reduced P300 amplitude in a visual oddball event-related potential task. A review of evidence bearing on the model is derived from findings from the Minnesota Twin Family Study, a population-based, longitudinal investigation of twin youth. These findings indicate that the collection of attributes related to behavioral disinhibition is familial, heritable, and interrelated. Evidence supporting P3 amplitude reduction (P3-AR) as an index of genetic vulnerability for this externalizing spectrum includes its association with (a) familial risk for substance use and antisocial personality disorders, (b) diagnoses of childhood disruptive disorders and substance use disorders, (c) early onset of undersocialized behavior, and (d) quantitative phenotypes related to externalizing problems. In addition, the development of substance use disorders over a 3-year period is associated with P3-AR measured prior to their expression. These findings suggest that P3-AR indexes one aspect of the genetic diathesis for a spectrum of externalizing problem behavior.

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1. Introduction

Almost 20 years ago, Begleiter et al. (1984) reported that the pre-adolescent sons of alcoholic men had reduced P3 amplitude in a visual oddball task, an effect that is also apparent in alcoholics themselves (e.g. Cohen et al., 2002; Glenn et al., 1996; Porjesz et al., 1987; Prabhu et al., 2001; Rodriguez Holguin et al., 1999a). In a meta-analysis of the literature that emerged in the decade following the publication of Begleiter et al., Polich et al. (1994) reviewed some 30 studies of the offspring of alcoholics and found that these investigations supported the findings from the original report. The meta-analysis indicated that diminished P3 amplitude was more pronounced for visual tasks, complex stimuli, and younger high-risk chil-
drug use and dependence, ASPD, nicotine dependence, and illicit other disorders, including childhood externalizing by the fact that alcoholism is often comorbid with other disorders that often co-occur (are comorbid) with substance use disorders, such as conduct disorder (CD, Bauer and Hesselbrock, 1999a,b), attention deficit hyperactivity disorder (ADHD, Brandeis et al., 2002; Johnstone and Barry, 1996; Klorman, 1991; Strandburg et al., 1996), and ASPD, Bauer, 1997; Bauer et al., 1994; Costa et al., 2000; O' Connor et al., 1994). Findings such as these have led to speculation that this putative endophenotype is not specific to familial risk for alcoholism or even for substance dependence generally (Bauer and Hesselbrock, 1999b). The specificity of P3-AR to alcoholism is further clouded by the fact that alcoholism is often comorbid with other disorders, including childhood externalizing disorders, ASPD, nicotine dependence, and illicit drug use and dependence (Kessler et al., 1997; Krueger, 1999b; Krueger et al., 1998; Kuperman et al., 2001). In addition, a shared vulnerability for these disorders is suggested by their aggregation in families (Bierut et al., 1998; Grove et al., 1990; Jang et al., 1995; Kendler et al., 1997; Kuperman et al., 1999; Pickens et al., 1995; Slutske et al., 1998; True et al., 1999; Tsuang et al., 1998). In P3 studies of alcoholics and their offspring, these disorders are often not systematically assessed, leaving unclear the degree to which the P3-AR effects attributed to alcoholism vulnerability might also be attributable to the presence of these comorbid disorders, either in alcoholic parents or in their high-risk offspring.

Ultimately, research on the etiology of alcoholism will be focused on the effects of specific genes. However, although genes related to the metabolism of alcoholism play a role in its genesis in Asian populations (Li, 2000), genes causing alcoholism or any psychiatric disorder have remained elusive. The complexity of the human genome, no doubt, contributes to the difficulty in identifying psychopathology-related genes, but our incomplete understanding of how best to define disorders (phenotypes) that capture the effect of gene action also complicates the task. While it would be desirable to have phenotype definitions that map to specific genes, the criteria used to develop definitions of psychiatric syndromes over the last 20 years have been driven much more by concerns about reliability than by etiologically based theory and research. This state of affairs has stimulated interest in correlated features of a disorder that may themselves be genetically influenced. Because they are less complicated than the heterogeneous constellation of behaviors used to define a psychiatric syndrome, it may be easier to uncover their genetic etiology. Included are endophenotypes, the biological basis of which may be more proximal to underlying genes. Also included are other quantitative traits, sometimes referred to as ‘intermediate’ and ‘alternative’ phenotypes.

Although these designations overlap and do not have precise definitions, intermediate phenotypes describe traits that emerge during development, preceding the onset of psychiatric disorder. They may be early expressions of the genetic predisposition to develop a specific disorder. Drug use or police contact at an early age constitutes such an attribute, signaling the later possible development of a substance use or antisocial personality disorder (ASPD). Alternative phenotypes refer to other facets of a disorder that may also reflect genetic effects such as those related to severity or course (e.g. heavy substance use, multiple arrests), specific symptoms (e.g. marked tolerance for a drug, repeated driving while intoxicated), and associated traits (e.g. personality characteristics). Quantitative phenotypes potentially confer increased power to...
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