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Gene-Environment Interplay in Alcoholism and Other Substance Abuse Disorders: Expressions of Heritability and Factors Influencing Vulnerabilities

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Factors that confer predisposition and vulnerability for alcoholism and other substance abuse disorders may be described usefully within the gene-environment interplay framework. Thus, it is postulated that heritability provides a major contribution not only to alcohol but also to other substances of abuse. Studies of evoked potential amplitude reduction have provided a highly suitable and testable method for the assessment of both environmentally-determined and heritable characteristics pertaining to substance use and dependence. The different personal attributes that may co-exist with parental influence or exist in a shared, monozygotic relationship contribute to the final expression of addiction. In this connection, it appears that personality disorders are highly prevalent co-morbid conditions among addicted individuals, and, this co-morbidity is likely to be accounted for by multiple complex etiological relationships, not least in adolescent individuals. Co-morbidity associated with deficient executive functioning may be observed too in alcohol-related aggressiveness and crimes of violence. The successful intervention into alcohol dependence and craving brought about by baclofen in both human and animal studies elucidates glutamatergic mechanisms in alcoholism whereas the role of the dopamine transporter, in conjunction with both the noradrenergic and serotonergic transporters, are implicated in cocaine dependence and craving. The role of the cannabinoids in ontogeny through an influence upon the expression of key genes for the development of neurotransmitter systems must be considered. Finally, the particular form of behaviour/characteristic outcome due to childhood circumstance may lie with biological, gene-based determinants, for example individual characteristics of monoamine oxidase (MAO) activity levels, thereby rendering simple predictive measures both redundant and misguiding.

Keywords: Gene; Environment; Interplay; Alcohol; Cocaine; MDMA; Personal attributes; P300 amplitude; Heritability; Self-control; Impulsivity; Antisocial personality; Executive functioning; Neurochemical substrates; Cannabinoids; Longitudinal influences; Vulnerability

INTRODUCTION

The urgency to characterise the genetic and environmental factors, not least in the necessity for prevention and intervention programs, has been of major importance for examinations of risk assessments for alcoholism and other substance abuse disorders (*cf.*, Bohman *et al.*, 1987; Johnson *et al.*, 1996). The search for genetic influences upon substance disorders has produced a flora of investigations implicating both specificity and generality of gene action (*e.g.*, van den Bree *et al.*, 1998a,b; Vanyukov and Tarter, 2000; Enoch and Goldman, 2001). For example, one major focus in the search for the etiology of alcoholism is centred on the effects of specific genes, *e.g.*, as implied by the gene action related to the metabolism of alcohol in Asian populations (Li, 2000). To some extent the study of specific phenotypes, *i.e.*, a defining substrate for the disorder, has proven effective for an elucidation of some aspects of causation. Thus, behavioural traits may describe phenotypes (these may have several designations, *e.g.*, 'endophenotypes', 'intermediate' or

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'alternative' phenotypes) that may precede disorder onset as early expressions of the genetic predisposition for alcoholism and/or other substance abuse. Phenotypes may refer to a multitude of facets pertaining to genetic 'make-up', like severity or course (chronic, heavy drug use, binge-drinking, or multiple drug arrests), symptom profiles (*e.g.*, tolerance, driving under the influence, cross-tolerance) and other traits, such as aspects of personality like impulsivity and lack of self-control. The study of quantitative phenotypes has thereby offered a means for gene identification (Boomsma and Dolan, 1998; Williams and Blangero, 1999; Williams *et al.*, 1999; Arya *et al.*, 2001). Albeit considerable, yet the genetic influence in alcoholism has not solely been the focus of clinical study but rather the role of gene-environment interplay has been a matter of major concern for over half-a-century (*e.g.*, Amark, 1951).

In the vein of genetic and biological liability, Heilig and Sommer (2004) have postulated that genetic factors contribute to alcohol dependence through two main categories of mechanisms: on the one hand, the 50%-60% heritability, observed in the disorder, has been presumed to be conferred by polymorphic variants, encoding functionally-altered proteins, or leading to differential transcriptional activity (see discussion on functional phenotypes by Le Moal *et al.*, 2004), and, on the other hand, the long-term changes during the process of dependence-addiction development may likely be accompanied and encoded by persistent changes in gene expression (Ilveskoski *et al.*, 2001; Mayfield *et al.*, 2002; Tabakoff *et al.*, 2003; Arlinde *et al.*, 2004). By this notion, genetic and environmental factors interact at the level of the transcriptome. Heilig and Sommer (2004) have applied differential display and Affymetrix oligonucleotide gene arrays to models of genetic susceptibility and alcohol-induced neuroadaptation. Several lines of observations by Heilig *et al.* (*e.g.*, Heilig *et al.*, 1989; 1994; Wahlestedt *et al.*, 1992; Thiele *et al.*, 1998; Heilig and Thorsell, 2002; Thorsell *et al.*, 2002) have found a neuromodulatory function of neuropeptide Y in the regulation of emotional behaviour and ethanol intake; in humans associations between a polymorphic allele of the prepro NPY gene (Kauhanen *et al.*, 2000; Zhu *et al.*, 2003) and the role of the neuropeptide in alcohol self-administration (Slawecki *et al.*, 2000; Badia-Elder *et al.*, 2001; Caberlotto *et al.*, 2001; Kelley *et al.*, 2001) are discussed. These studies depict an 'outsider' in the alcoholism-substance abuse-personality disorder configuration, discussed below, and must contribute to the equation underlying disease vulnerability.

A different strategy for investigating genetic susceptibility has been offered by the focus upon the TaqIAI allele of the DA receptor gene D_2 (*DRD2*) that has been associated with alcoholism and addictive behaviour (Blum *et al.*, 1990; Cook *et al.*, 1992; Comings *et al.*, 1994; 1996; Hill *et al.*, 1998; Noble, 2000) as well as problems of personality (Ponce *et al.*, 2003). The examination of dopaminergic genes in alcoholism is an essential ingredient of gene-environment interplay in the disorder and may elucidate the identification of genetic subgroups among afflicted individuals (Cloninger *et al.*, 1988; Cloninger, 1991; Babor *et al.*, 1992; Cook *et al.*, 1992). Ponce *et al.* (2004) observed that the presence of the TaqIAI allele in the *DRD2* genotype in Spanish alcoholics is associated with higher concentrations of homovanillic acid (HVA) in urine when compared with patients homozygous for the *TaqI*AI allele. The sample of 142 Spanish male alcoholic patients was divided into two groups on the basis of the presence/absence of the A1 allele in their genotype. Urine samples, following HPLC analysis, revealed significant differences of HVA concentrations between the two patient groups, implying that this polymorphism may be related to the variance of urine HVA levels, which seems consistent with other evidence associating the *TaqI*AI allele with other dopaminergic characteristics (Gabbay *et al.*, 1996; Miyake *et al.*, 1999).

ALCOHOL-INDUCED VIOLENCE AND EXECUTIVE FUNCTION

The implications of alcoholism are far-reaching: interpersonal aggression is facilitated by the drug (Bushman and Cooper, 1990; Chermack and Giancola, 1997), with ever-increasing crime statistics (*e.g.*, Collins and Messerschmidt, 1993; Spunt *et al.*, 1995a) and an alarming degree of ubiquity over gender (Spunt *et al.*, 1990; Buss *et al.*, 1995), age (Gleason-Milgram, 1993; Dembo *et al.*, 1997), ethnic/racial background (Valdez *et al.*, 1995) and geography (Murdoch *et al.*, 1990). Alcohol facilitation of the expressions of aggression include, for example: aggressive threat (Choquet *et al.*, 1991), verbal aggression (Babor *et al.*, 1983), marital and family violence (Leonard and Jacob, 1988; Leonard and Senchak, 1996), sexual aggression (Parks *et al.*, 1996), child abuse (Kaufman-Kantor and Strauss, 1990), use of handguns (Brent *et al.*, 1987), murder (Klatsky and Armstrong, 1993) and suicide (Brent *et al.*, 1987). Recent notions on the acute and long-term effects of alcohol pertain to its disruptive influence upon 'executive functioning', not only with regard to the expression of aggression but also regarding other aspects of function and personality (Hull and Bond, 1986; Bushman, 1993; 1997; Seto and Barbaree, 1995; Giancola *et al.*, 1996; Ito *et al.*, 1996). For example, Pihl *et al.* (1993) imply that acute alcohol disturbs prefrontal cortex-hippocampal function, through its anxiolytic effects, eliminating signals of punishment thereby contributing to behavioural disinhibition, concurrent with enhanced aggressive responses through the transient psychomotor effects of the drug and increased sensitivity to physical pain signals. The prefrontal cortex subserves a diversity of cognitive, executive functions, including: selective attention (in conjunction with the anterior cingulated cortex (see Palomo *et al.*, 2004), as well as the amygdala and hypothalamus (Damasio and Anderson, 1993), in the context of emotional behaviour, bearing in mind the 'frustration' construct (Archer, 1988), strategic planning, hypothesis generation, abstract reasoning, temporal ordering and the sequencing and organisation of information in working memory (Milner and Petries, 1984; Stuss and Benson, 1984; Kimberg and Farah, 1993; Lezak, 1995). Executive function may be described as a cognitive propensity to carry out effective planning, initiation and regulation of goal-directed behaviour (see also Shallice, 1982; Benson, 1993), and is involved in the expression of aggressive behaviour (Moffitt, 1993; Giancola, 1995; Morgan and Lilienfeld, 2000), particularly alcohol-related aggression (Hoaken *et al.*, 1998). Poorer performance on neurophysiological estimates of executive functioning, compared with nonexecutive functioning, is observed in individuals presenting symptoms characterised by aggression, such as antipersonality disorder (Gorenstein, 1987; Malloy *et al.*, 1990), psychopathy (Smith S *et al.*, 1992; Lapierre *et al.*, 1995), conduct disorder (Lueger and Gill, 1990), delinquency (Yeudall *et al.*, 1982), attention deficit hyperactivity disorder (Benson, 1991; Barkey, 1997) and inattention-overactivity problems (McBurnett *et al.*, 1993), implicating regional glucose metabolism (Volkow and Tancredi, 1987; Volkow *et al.*, 1990; 1995a,b). It is interesting to note that psychiatric patients arrested for violent crimes, but not those arrested for non-violent crimes showed executive functioning deficits (Krakowski *et al.*, 1997). Alcohol exerts profound effects upon executive function (Oscar-Berman and Hutner, 1993; Evert and Oscar-Berman, 1995), disrupting attention, planning, judgement, organisation, cognitive flexibility and appraisal, behavioural inhibition, abstract reasoning, set shifting and working memory (Zeichner *et al.*, 1982; Peterson *et al.*, 1990; Lyvers and Maltzman, 1991; Arbuckle *et al.*, 1994; Post *et al.*, 1996; Mulvihill *et al.*, 1997). Giancola (2000) has proposed a framework of executive functioning mediating alcohol-related aggression that merges with notions of gene-environment interplay assembling a phenotype beyond acute, environmental factors to long-term genetic susceptibility. Thus, it is proposed that (a) executive functioning mediates the alcohol-aggression relation whereby acute alcohol disrupts executive functioning which in turn facilitates expressions of aggression, (b) individuals with low levels of executive functioning (see below) lack the moderating influence of executive functioning upon the alcohol-aggression relation are facilitated by alcohol in their expression of aggressive behaviour. Taking into account the long-term effects of alcohol on glutamate signalling in brain development (Guerri *et al.*, 2001; Guerri, 2002; Olney *et al.*, 2002a,b), the major liability leading to loss of normal executive functioning becomes progressively more pronounced (*e.g.*, Moghaddam, 2003; 2004; Fredriksson and Archer, 2004).

PREDISPOSITION, HERITABILITY AND P300 AMPLITUDE REDUCTION

Studies of P300 event-related potential amplitude have documented a vast array of evidence implicating the unique gene-environment interplay in the vulnerability for substance use disorders. In this context, it was reported originally by Begleiter *et al.* (1984) that the pre-adolescent sons of male alcoholics showed reduced P3 amplitude in a visual oddball task set up to analyse event-related potentials. This reduced P3 amplitude reduction is evidenced in alcoholics themselves (*e.g.*, Poresz *et al.*, 1987; Glenn *et al.*, 1996; Prabhu *et al.*, 2001; Cohen *et al.*, 2002). Polich *et al.* (1994) performed a meta-analysis of 30 studies on the offspring of alcoholics; it was shown the reduction in P3 amplitude was more marked for visual tasks, complex stimuli, and younger high-risk children. The degree of heritability of event-related brain potentials is evidenced not least of all in families with a history of alcoholism (Almasy *et al.*, 1999; 2001), and further exemplified by the association between parental alcoholism and the diminished P3 amplitude outcome was underlined in a large number of subsequent studies (*e.g.*, Cohen *et al.*, 1993; Hill *et al.*, 1995; 1999; Ramchandra *et al.*, 1996; Ramsey and Finn, 1997; van der Stelt *et al.*, 1998; van der Stelt, 1999; Hada *et al.*, 2001). Thus, it has been suggested that the P3 amplitude reduction may serve as an endophenotype providing a laboratory measure of genetic risk for development of alcoholism (Iacono, 1998; Begleiter and Porjesz, 1999). Applying the Minnesota Twin Family Study Cohorts, described as an ongoing, state-wide study of pre-adolescent and late adolescent twins and their parents (*cf.*, Iacono *et al.*, 1999; see also Iacono *et al.*, 2002), a review of the evidence from a population-based, longitudinal investigation of twin youth has been carried out by Iacono *et al.* (2003). Their findings demonstrated also that a particular assembly of attributes associated with behavioural disinhibition (see also Barkley *et al.*, 1992; Barkley, 1997) was distinguished in being familial, heritable and interrelated. In this regard, it is necessary to consider the contributions of gene-environment interplay to expressions of behavioural disinhibition to substance disorders and problems of personality (Young *et al.*, 2000), not least regarding the genetic analysis of alcoholism and personality characteristics (Czerwinski *et al.*, 1999). The presence of P3 amplitude reduction in individuals indicated several deviations from normal behaviour and provided an index of genetic vulnerability for 'externalizing spectrum' including: (1) familial risk for substance use and antisocial personality disorders, (2) diagnoses of childhood disruptive disorders and substance use disorders, (3) the early onset of 'under-socialized' behaviour, and (4) quantitative phenotypes related to externalising problems, *e.g.*, alcohol and other substance abuse, criminal behaviour, and aggression.

With reference to the alcohol/abused substance association to aggressiveness, this reduced/attenuated P300 amplitude is observed too in male prison inmates with histories of violent behaviour (Drake *et al.*, 1988; Barratt *et al.*, 1997), and in adolescent psychiatric patients with elevated levels of verbal and physical aggression (Harmon-Jones *et al.*, 1997). Further, individuals with antisocial personality disorder showed reduced P300 amplitude selective to the frontal scalp region (Hesselbrock *et al.*, 1993; Bauer *et al.*, 1994; O'Connor *et al.*, 1994; Bauer, 1997). It is of interest to note that (i) reduced frontal P300 amplitude is associated with poor executive, but not nonexecutive, functioning, and (ii) the prefrontal cortex is one area considered to generate P300 amplitude (Ruchkin *et al.*, 1990; Yamaguchi and Knight, 1991; Johnson, 1993; Alexander *et al.*, 1995). These studies taken together with those relating alcohol-induced aggression to executive functioning (above) and others implicating an intimate and complex relationship between genetic vulnerability in personality problems and substance abuse imply an intricate framework within which alcoholism and other substance abuse delve deep into the underpinnings of gene-environment interplay.

Much evidence for heritability for problems associated with substance abuse may be derived from a number of other twin studies (*e.g.*, Grove *et al.*, 1990; Kendler *et al.*, 1992; Scherrer *et al.*, 1996; Maes *et al.*, 1999; Prescott *et al.*, 1999), besides those observed from the Minnesota Twin Family Study. For example, Kendler *et al.* (1999a,b) obtained substantial genetic influences on the initiation of substance use and additional influences on the transition to substance abuse in a female sample. These findings were replicated in a separate study of male twins (Kendler *et al.*, 2000) wherein the degree of heritability was found to be 35% for any drug use and 83% for heavy drug use (but see also Prescott and Kendler, 1999). The common genetic variation between drug and alcohol abuse/dependence is clearly a recurring theme. Nevertheless, twin study results are neither simple, straightforward or amenable to easy interpretations: in a twin study of Vietnam-era service (Tsuang *et al.*, 1999), although genetic influences for extent of marijuana use were obtained, heritability decreased with heavier use and the transition from abuse to dependence, and genetic influences were non-significant for other drugs except for amphetamines and cocaine. In agreement with the major consensus from twin studies, Kendler and Prescott (1998) described significant genetic influences upon heavier cannabis use and the environmental implications for any debut into cannabis usage. Nevertheless, the salient distinctions and specificity of genetic and environmental risk factors in addiction are evident also from these studies (*cf.* Kendler *et al.*, 2003). Thus, the all-important interplay between gene and environment may not be reiterated often enough (*cf.*, Cadoret, 1992; Cadoret *et al.*, 1986; 1995; 1996; Heath *et al.*, 1997), as appears relevant in a constellation of other neuropsychiatric disorders whether with drug co-morbidity (Miles *et al.*, 2002) or without (Cadoret *et al.*, 1983; 1985). In clinical terms, alcoholism is a chronically relapsing disorder, and over the life-span of alcoholics, who may/may not intermittently display a variety of personality and/or character defects, cycles of ethanol/other substance intoxication may alternate periodically with intervals of abstinence, with one likely consequence that a withdrawal syndrome whose severity is correlated positively with the incidence of intoxication and withdrawal cycles is to be observed (Brown *et al.*, 1988).

PERSONAL ATTRIBUTES PREDICTIVE FOR SUBSTANCE USE/ABUSE

In view of incremental budgets required to stem the tide of social and clinical problems, much effort has been invested upon the identification of factors associated with individuals' vulnerability and eventual predisposition towards substance abuse. Although the contribution of personality factors has been considered, both intuitively and explicitly, the last half-dozen years have reinforced the notion that personal characteristics interplay markedly in the eventual risk for sooner or later substance abuse (Galen *et al.*, 2000; Helmus *et al.*, 2001; Koehl *et al.*, 2002; Palomo *et al.*, 2002; Wolff and Wolff, 2002). For example, Corr and Kumari (2000) studying individual differences in self-reported mood following either 5 mg or 10 mg D-amphetamine challenge tested the modifying role of Eysenck's psychoticism, Cloninger's novelty-seeking and Depue and Collin's extraversion in a double-blind study. They found significant psychoticism x D-amphetamine interactions for both drug doses, expressed by increased energetic arousal and hedonic tone but reduced tense arousal in low psychoticism individuals but *vice versa* in high psychoticism individuals, whereas neither novelty-seeking nor extraversion modified the effects of D-amphetamine. Two implications (although there are several others) may be relevant to present purposes: (1) routine inclusion of personality measures is integral to psychopharmacological studies, and (2) affective state appears to modulate the eventual expression of the rewarding entity (*cf.*, Palomo *et al.*, 2004). In this connection, it appears that personality disorders are highly prevalent co-morbid conditions among addicted individuals, and, this co-morbidity is likely to be accounted for by multiple complex etiological relationships (Skinstad and Swain, 2001; Verhuel, 2001; Conway *et al.*, 2002; Flory *et al.*, 2002), not least in adolescent individuals (Chabrol and Armitage, 2002). Much effort has been invested too in the enterprise involving prediction of risk for future substance abuse from assessment of personality characteristics (Crowley *et al.*, 1998; Comeau *et al.*, 2001; Conway *et al.*, 2002; Young *et al.*, 2002; Sussman *et al.*, 2003). Recently, Langbehn *et al.* (2003) using survival analysis methodology, confirmed that risk for substance abuse and substance-related problems was increased, not only in comparison with adoptees without known biological risk but also adoptees with biological risk for only one disorder, when combined when antisocial personality and substance abuse occur in the same parent. The authors imply that the biological associations presented in the study are consistent with generalization to other substances of an alcoholism phenotype similar to Cloninger's Type II or Babor's Type B (see below); this implication of *dual* gene-environment interactions is central to any consideration of drug-related disorders.

The notion of 'self-control' has been considered periodically with respect to the involvement of personality in substance abuse disorders. Lack of self-control is suggested to be central to individuals' drug involvement (Gottfredson and Hirschi, 1990; Jackson *et al.*, 2000). Furthermore, lack of self-control among juveniles has been found to be a significant predictor for serious alcoholism, tobacco use and other substance usage, as well as a cluster of other felonies (*e.g.*, Wills *et al.*, 1995; 1999; 2000; Longshore *et al.*, 1996; Longshore, 1998; Griffen *et al.*, 2000; Sher *et al.*, 2000). In this regard, Sussman *et al.* (2003; but see also Sussman and Dent, 1996; Sussman *et al.*, 1997; 1999; 2000; 2001) have found that the most consistent concurrent predictors of substance use were male gender, antisocial personality disorder and social self-control. Their results have identified social self-control, whereby lack of self-control refers to the inability to consider the consequences of one's action before acting, as a unique concurrent predictor for substance abuse. Associated with the issue of a self-control deficient personality in substance abuse, is the prevalence of pathological gambling in individuals with both alcohol and other drug problems (*e.g.*, Lesieur *et al.*, 1986; Castellani and Rugle, 1995; Feigelman *et al.*, 1995; Spunt et al, 1995; Castellani *et al.*, 1996; Daghestani *et al.*, 1996; McCormick *et al.*, 1997). For instance, Steinberg *et al.* (1992) studied gambling problems in 298 cocaine abusers seeking treatment that evidenced a 15% prevalence rate for pathological gambling. On the other hand, up to 50% of pathological gamblers present a history of drug or alcohol use disorders (Ramirez *et al.*, 1983). The personality trait, impulsivity, is associated too with substance use and abuse, as shown by both longitudinal (White *et al.*, 1994; Dawes *et al.*, 1997) and cross-sectional (Jaffe and Archer, 1987) studies. Thus, a multitude of studies on patient populations have indicated that substance-abusing individuals score higher than controls on personality inventories of impulsivity (Eisen *et al.*, 1992; Chalmers *et al.*, 1993; Cookson, 1994; Allen *et al.*, 1998).Certainly, the implications of impulsivity for numerous aspects of behaviour are not to be neglected (Eysenck and Eysenck, 1978; Eysenck and McGurk, 1980; Eysenck *et al.*, 1985). Besides its association with substance abuse, impulsivity may be related to several other problem areas including criminal activity, fire-setting and repeated aggression (Stanford and Barratt, 1992) although levels of impulsivity in pathological gambling appear to vary (Allcock and Grace, 1988; Carlton and Manowitz, 1994; Blaszczynski *et al.*, 1997; Steel and Blaszczynski, 1998), as confirmed specifically in a recent study by Petry (2001).

There is now an extensive documentation covering the epidemiological and functional background of children born to and brought up within a parental environment marked by alcoholism or other substance disorders (*e.g.*, Windle and Searles, 1990; Chassin *et al.*, 1993; US Department of Health and Human Services, 1994; Clark *et al.*, 1997; Windle, 1997; Johnson and Leff, 1999; Kumpfer, 1999; McGue *et al.*, 2001). For example, parental substance abuse may take the form of neurochemical metabolite alterations in the young male offspring (Gabel *et al.*, 1995). The risk factor inherent to this environment is considerable since these children are four to six times more likely to develop alcohol problems during their lifetimes (Russell, 1990), show an over-representation of both internalising (*e.g.*, anxiety, depression) and externalising (*e.g.*, conduct disorders, alcohol use, substance use) disorders (Seilhamer and Jacob, 1990), as well as risk for fetal alcohol syndrome (Larkby and Day, 1997) and inadequate parenting plus negative parent-child interactions (Jacob and Johnson, 1997). Fals-Stewart *et al.* (2003) have identified several predictors for these destructive interactions including: the frequency of male-to-female physical aggression between the parents, the frequency of the father's substance use/abuse during the previous year, diagnosis of antisocial personality disorder of the fathers, and mother's level of psychological distress. There appears to be also a three-fold higher risk for alcohol abuse/dependence in the children of alcoholics (Schuckit, 1998; but see also Clark *et al.*, 2004), and clinical syndromes expressed by conduct/oppositional problems, abstract reasoning impairments, memory and goal-directed behavioural deficits, problems in personal and social functioning, and excessive aggressiveness (Zucker and Fitzgerald, 1991; Noll *et al.*, 1992; Reich *et al.*, 1993; Pihl and Bruce, 1995; Carbonneau *et al.*, 1998). Finally, several longitudinal studies underline the co-morbid incidence of dysfunctional behavioural traits and substance abuse disorders (Kopstein *et al.*, 2001; Adalbjarnardottir and Rafnsson, 2002; Gorman and Derzon, 2002).

Certain twin studies imply a partially shared heritability, somewhat in the form of a 'clustering' of traits, for combinations of personality disorders and conduct disorder (Slutske *et al.*, 1998; van den Bree *et al.*, 1998b; True *et al.*, 1999; Jang *et al.*, 2000). Familial clustering of these traits may offer several lines of evidence predisposing genetic and environmental factors, including: (a) high rates of character disorder in the first degree relatives of alcoholics (Amark, 1951; Bleular, 1955), (b) a higher incidence of familial alcoholism in military men with antisocial behaviour and more severe alcoholism (Frances *et al.*, 1980), (c) a higher incidence of aggressiveness in the fathers of criminal alcoholics (McCord, 1981), (d) a younger age of onset and greater legal problems in familial alcoholism, particularly if both parents were alcoholics (McKenna and Pickens, 1981; Schuckit, 1984), (e) a family history of alcoholism, in males, was associated with earlier onset, greater severity, and antisocial behaviour in a large sample of hospitalised alcoholics (Latcham, 1985), (f) an A/B typology (Babor *et al.*, 1992), with type B resembling strongly the Type II alcohol of Cloninger (*cf.*, Cloninger *et al.*, 1981; Cloninger, 1987; Schuckit and Irwin, 1989), as well as the further clustering evidence reinforcing personality-substance abuse interactions (Litt *et al.*, 1992). For example, in families with a substance-abusing father, there was a significant correlation between parental disruptive behaviour (whether as child or adult) and similar behaviour in 10-12 year-old sons (Majumder *et al.*, 1998). In the context of these notions of 'cluster' and in conjunction with thread of impulsivity (see above, it ought to be noted that several of these problems may be associated with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) or childhood psychopathy, whether drugs involved are alcohol or other compounds (West and Prinz, 1987; Mannuzza *et al.*, 1993; Biederman *et al.*, 1995; Levin and Kleber, 1995; Milberger *et al.*, 1997; Disney *et al.*, 1999). Thus, the co-morbidity of substance use disorders with both hyperactivity and aggressiveness syndromes has been discussed for over two decades (*e.g.*, Loney *et al.*, 1980). Furthermore, the co-morbidity of personality disorders (and other 'mental' disorders) with alcohol and other substance abuse must not be overlooked (Regier *et al.*, 1990; Tyrer *et al.*, 1997; Nadeau *et al.*, 1999; Janowsky *et al.*, 2001; Verheual, 2001). Nevertheless, the issue of contributory parental disorders other than substance abuse disorders or parental socio-economic status and general life functions was addressed by Schuckit *et al.* (2000) who found that once familial antisocial disorders and socio-economic status was controlled for, a family history of alcoholism did not relate to childhood externalising disorders.

PERSONALITY, HPA AXIS AND STRESS IN SUBSTANCE ABUSE DISORDERS

The complex and multiple interactions of personality attributes with the various dimensions of hypothalamic-pituitary-adrenal (HPA) axis mobilization appear to orchestrate the eventual behavioural outcome of substance use in a variety of ways, depending on the particular class of substance administered (Goeders, 2002; Le Moal *et al.*, 2004), and in the final analysis offer critical determinants of vulnerability for addictive behaviour (Majewska, 2002). The involvement of the HPA axis in alcoholism has been established, whereas in the present case interest is focussed on this axis in users of the drug methylenedioxymethampetamine (MDMA, or "ecstasy"), not only for the serotonergic implications (*cf.*, Ricaurte *et al.*, 2002; Van Praag, 2002) but the "in-drug" status of the compound. Thus, in laboratory studies, MDMA users showed high levels of both cortisol and adrenocorticotrophic hormone (ACTH) but low levels of experimental aggressiveness compared to normal control subjects (Gerra *et al.*, 2001). The compound is known to elevate both cortisol and ACTH in humans (Grob *et al.*, 1996; Mas *et al.*, 1999). As noted above, HPA axis hyperactivity and reduced reactivity to stressful events in conjunction with brain serotonergic and other neurotransmitter imbalance (Gerra *et al.*, 1998; 2000; Kish *et al.*, 2000; Fox *et al.*, 2001; Mayerhofer *et al.*, 2001; Parrott *et al.*, 2001; Parrott, 2002) presents a recognizable formula for depressive states (Drevets *et al.*, 1997; Rao *et al.*, 1999). DA functioning may be impaired also in MDMA users (Gerra *et al.*, 2002), since drugs enhancing DA neurotransmission mobilize the HPA axis (Mokrani *et al.*, 1995). Recently, Gerra *et al.* (2003) examined the level of HPA axis mobilization, under both basal and stressful conditions, growth hormone responses to bromocriptine, the DA D_2 receptor agonist, intervention, and psychometric analysis of personality variables. They found significantly higher basal levels of cortisol and ACTH, accompanied by blunted reactivity, *i.e.*, lower levels of cortisol and ACTH, under stress, in the MDMA users. DA D_2 receptor sensitivity, as assessed by growth hormone response to bromocriptine, was reduced also in the MDMA users. The HPA axis reactivity correlated directly with growth hormone responsiveness but inversely with the psychometric measures of aggressiveness and 'novelty-seeking'. Their results appear to present a fateful pattern: unhealthy over-mobilization of a basal HPA axis (accompanied by a plethora on neurodegenerative consequences for highly sensitive brain regions that modulate its function) is exacerbated by suppressed reactivity under conditions where the axis ought to be activated, blunted DA-system engagement, and personality-driven behavioural outcomes of a maladaptive nature. Tragically, this pattern must constitute an equation with self-destructiveness as its product.

MONOAMINE TRANSPORTER MECHANISMS IN BEHAVIOURAL SENSITIVITY

Neurotransmitter reuptake mechanisms remain basal to any consideration of the mechanisms involved in the psychostimulant and rewarding properties of cocaine, since the drug potentiates the neurotransmission of DA, noradrenaline (NA) and serotonin (5-HT) at synaptic terminals (*e.g.*, Ross and Renyi, 1969; Heikkila *et al.*, 1975; Hadfield *et al.*, 1980). There exists a strong relationship between binding to the DA transporter and the functional effects of the drug (Kula and Baldessarini, 1991; Boulay *et al.*, 1996; Sora *et al.*, 2001). Izenwasser (2004) describes a wide range of studies, using chronic drug administration procedures that focus upon the role of the DA transporter in cocaine abuse. These studies, that administered either cocaine or selective inhibitors of the DA transporter (*e.g.*, GBR 12909 or RTI-117), NA transporter (*e.g.*, desipramine), or 5-HT transporter (*e.g.*, fluoxetine), have produced evidence that although selective DA uptake inhibitors have the propensity to induce sensitisation to cocaine, the long-lasting sensitised response to a cocaine challenge, observed in cocaine-pretreated rats, may be due to cocaine action on a neurotransmitter system other than, or in addition to DA (see Kalivas *et al.*, 1988; Izenwasser and Cox, 1992; Izenwasser *et al.*, 1999; Collins and Izenwasser, 2002). Behavioural sensitisation is induced by intermittent chronic (continuous) administration of the drug, providing a progressive enhancement over the length of the administration and is expressed when the animals receive a drug challenge (cocaine) even long after withdrawal from the chronic administration (King *et al.*, 1992; Sorg and Ulibarri, 1995; Kalivas and Duffy, 1998; Partridge and Schenk, 1999). It appears that although DA remains one critical component for behavioural and addictive properties of cocaine the contributions of other neurochemical substrates are to be attended. In this regard, it may be worthwhile to consider the central role of glutamate in processes that underlie the development and maintainance of addictive behaviours, *e.g.*, reinforcement, sensitization, habit learning, contextual learning, craving and relapse. It has been shown that many of the actions of glutamate achieve their essential significance through a stimulatory interaction with dopaminergic systems, and certain glutamatergic mechanisms contribute to addictive behaviours independent of dopaminergic mechanisms (for review, see Tzschentke and Schmidt, 2003).

As described by Kalivas (2004) and others (Vanderschuren and Kalivas, 2000) and in accordance with different avenues of evidence indicated above, cocaine addiction too appears to be the result of alterations in brain functioning due to gene-environment interplay, reflected by genetic vulnerability and environment circumstance, modulated by pharmacological status. The reduction in Homer protein, encoded by three genes (Homer 1-3) and involved in aspects of glutamate signalling in the nucleus is one change effected by repeated cocaine administration on glutamate neurotransmission (*e.g.*, Swanson *et al.*, 2001). Kalivas *et al.* (2004) have presented the behavioural and neurochemical effects of *Homer2* deletion in mice; these alterations are compared also with the effects of cocaine administration to rats. In a series of studies, Kalivas *et al.* (Kalivas and Duffy, 1993; Pierce *et al.*, 1996; Vanderschuren and Kalivas, 2000; Baker *et al.*, 2003; McFarland *et al.*, 2003) and others (Horger *et al.*, 1990; Schippenberg and Heidbreder, 1995; Heidbreder *et al.*, 1996; Reid and Berger, 1996) have compared the effects of *Homer2* gene deletion in mice (here they compared wild-type with *Homer2* knock-out mice on several measures related to glutamate transmission in the nucleus accumbens and cocaine-induced behavioural changes) with withdrawal from repeated cocaine administration in rats on cocaine-induced behaviour and neurochemistry in the nucleus accumbens. It was shown that, in each case, *i.e. Homer2 vs* wild-type and repeated cocaine *vs* saline, locomotor activity was increased, conditioned reward was increased, acquisition of self-administration was increased, and cocaine-induced glutamate was increased, whereas basal glutamate was decreased, and basal DA showed no difference. For cocaine-induced DA there was no difference for *Homer2 vs* wild-type whereas for repeated cocaine *vs* saline there was an increase. An essential message from these studies appears to be: *Homer2* gene deletion in mice appears to give rise to a phenotype that is remarkably similar to the phenotype produced by repeated cocaine administration in rats.

Fernandez-Ruiz *et al.* (2004) have described how the cannabinoids, through a diversity of mechanisms that influence the neurodevelopment of brain structure and function, affect the ontogeny of various neurotransmitter systems (Fernandez-Ruiz *et al.*, 1999; Ramos *et al.*, 2002; Mato *et al.*, 2003), leading to changes in different behavioural patterns. They present a number of lines of evidence implicating the role of the endocannabinoid signalling system during brain development, including the presence of element early in the foetus, the location of these elements in particular structures, and the presence of an obvious functionality at early ages (see also Fernandez-Ruiz *et al.*, 2000). The endocannabinoids and their receptors influence the expression of key genes for neural development: (a) tyrosine hydroxylase (Bonnin *et al.*, 1995; 1996; Hernandez *et al.*, 1997; 2000), (b) proenkephalin, the opioid precursor (Manzanares *et al.*, 1999; Perez-Rosado *et al.*, 2000), (c) the neural adhesion molecule, L1 (Gomez *et al.*, 2003), and (d) the Bcl-2/Bax system involved in apoptosis regulation during brain development (Maccarrone and Finazzi-Agro, 2003). Taken together, these diverse yet converging avenues provide much support for notions of far-reaching consequences of endocannabinoid mechanisms contributing to sufficiency of components necessary for normal brain development.

GABAergic PROCESS IN ANTI-ALCOHOL THERAPY

As indicated by Colombo *et al.* (2004a), the putative application of pharmacological agents in the treatment of alcoholism and alcohol dependence may provide an important adjunct to other therapeutic measures in the achievement of drug abstinence, thereby facilitating the psychosocial supportive and rehabilitative interventions. They review the evidence obtained from preclinical and clinical investigations designed to assess and describe the potential characteristics of the $GABA_B$ receptor agonist, baclofen, to induce alcohol-rejection (expressed by the authors as 'anti-alcohol properties, a term that is adopted here too) and thereby the eventual GABAergic involvement in alcoholism (Smith BR *et al.*, 1992). The genetic inference for the preclinical studies is derived from the use of the Sardinian alcohol-preferring rats whose ethanophilic characteristics, incrementally consolidated over many generations, have been established in the laboratory (*cf.*, Colombo *et al.*, 1995; 1998; 2002; 2004b,c; Agabio *et al.*, 1996; 2000; Vacca *et al.*, 2002). Colombo *et al.* (2000), initially, observed that baclofen, administered i.p. in the dose range of 2.5-10 mg/kg, induced a more or less dose dependent reduction of alcohol intake. Further studies established both the propensity of the anti-alcohol agent to suppress the alcohol deprivation effect and its effects in suppressing motivation to consume alcohol (see also File *et al.*, 1991; Smith BR *et al.*, 1999; Colombo *et al.*, 2003a,b). It is interesting to note (with regard to the above discussion on DA transporter mechanisms in cocaine addiction) that baclofen was found to be effective in the antagonism of nicotine-, cocaine-, and morphine-induced DA release in the rat nucleus accumbens (Fadda *et al.*, 2003), in the context of current notions of DA as reward and motivational substrate (Spanagel and Weiss, 1999; Weiss and Porrino, 2002; Weiss *et al.*, 1993). Colombo *et al.* (2004a) describe also the findings of several clinical investigations to establish the anti-alcohol properties of baclofen. For example, Addolorato *et al.* (2002a) carried out a double-blind study on 39 alcoholic patients that assessed the effects of baclofen on the consumption of alcoholic beverages and on alcohol craving, and it was shown that a greater proportion of the patients that received baclofen, compared with the placebo-treated group, both completed the study and achieved and maintained complete abstinence during the 4-week period. These results are presented in detail (Colombo *et al.*, 2004a). In a separate study, Addolorato *et al.* (2002b) assessed the effects of baclofen upon the severity of the alcohol withdrawal syndrome and it was observed that the $GABA_B$ agonist abolished these symptoms in all the patients; furthermore, the compound was found efficacious in suppression of delirium tremens (Addolorato *et al.*, 2003). Although these latter results pertaining to GABAergic mechanisms (a generally inhibitory neurotransmitter) in the complex range of expressions associated with alcohol withdrawal (and a major contributory factor in the difficulties related to the treatment of the disorder), it is necessary to bear in mind the glutamate antagonist action of alcohol at higher doses and the increased glutamatergic neurotransmission (a generally excitatory action) involved in the alcohol withdrawal hyperexcitability condition (Krystal *et al.*, 2003) where the actions of baclofen have been implicated (Misgeld *et al.*, 1995).

The complexities of gene-environment interplay defy any attempts to achieve a semblance, nevertheless in the context of the substance abuse-personality disorders, discussed above, it may of relevance to review certain outcome possibilities in the cycle of violence in maltreated children. Thus, Caspi *et al.* (2002) studied male children from birth to adulthood to address the question: why do some maltreated children grow up to develop antisocial behavioural whereas others do not? It was shown that a functional polymorphism in the gene encoding monoamine oxidase-A (MAO-A) was found to moderate the effect of maltreatment. Maltreated child with a genotype that conferred high levels of MAO-A expression were less likely to develop antisocial problems. These intriguing results offer epidemiological indications that genotype can modulate vulnerability of an individual to severe environmental insults. It may be borne in mind the significant association between platelet MAO activity behaviour/personality, voluntary alcohol intake and neurochemical measures of serotonergic activity (Oreland *et al.*, 2002a,b).

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