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Review

How gene–stress–behavior interactions can promote adolescent alcohol use: The roles of predrinking allostatic load and childhood behavior disorders

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Abstract

A variety of environmental and genetic factors modulating the risk for alcoholism have been described, which predominantly act by interacting with each other. For example, the family, peers and society determine the level of exposure to stress and alcohol, while genes modulate how sensitive an individual responds to both. The resulting behaviors feed back to the social environment, modulating and in the worst case increasing further stress exposure.

We here review neurobiological evidence how such a process of mutual interaction can involve and affect drinking. In at-risk adolescents it may have been in force for many years before they have their first alcoholic drink, increasing their risk for addiction by generating allostatic load. As an example, psychiatric disorders involving attention deficit, hyperactivity, or disruptive behaviors first evolve during childhood and are influenced by all the above factors. They are also strongly associated with harmful adolescent drinking and later alcohol use disorders.

One important implication of this concept is that issues such as family adversity, adolescent psychiatric disorders, or adolescent drinking might not only be associated with, but causally related to, the risk for later addiction. They are targets for preventive interventions, which should start as early as possible in subjects at-risk.

Keywords: Stress; Genes; HPA system; Alcohol; Adolescents; Addiction; Disruptive behavior; Attention deficit; Hyperactivity

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1. Introduction

Inappropriate alcohol use in adolescents is a growing problem in virtually all western countries. Binge drinking, for example, is increasingly common and occurs at younger ages than used to be. There is good reason to assume that adolescent alcohol use can be harmful for brain development (Hiller-Sturmhöfel and Swartzwelder, 2005; Tapert et al., 2005; Nagel et al., 2005; Monti et al., 2005). Why adolescent drinking habits changed so quickly during the last decades remains largely unknown. In adults, stress and genes can promote alcohol drinking as well as the development and maintenance of dependence. These two risk factors were long viewed as acting independently from each other. The idea of gene–environment-interactions as a relevant mechanism emerged only recently (see Rutter, 2002 for review) and was adapted to studies on alcoholism (Cutrona et al., 1994; Jacob et al., 2001). Virtually all factors that influence alcohol drinking and dependence interact with each other, very often vice versa, sometimes forming feed-forward loops as in a vicious circle. As a classical example, too much drinking can give rise to psychosocial stress due to conflict with families, employers, or the law, while stress can in turn promote more drinking. In adults having developed alcohol dependence, only the result of a longstanding process can be observed. What cannot be seen is how a multitude of risk factors and protective factors mutually interacted over time to influence behavior in a way that ultimately led to addiction.

This paper will review evidence for the concept that such a process can already be effective since birth and throughout childhood, since factors including early childhood trauma, personality traits, family adversity, parental drinking, and disorders involving attention deficit, hyperactivity and social functioning are associated with later alcohol use disorders (AUD). During adolescent development, peers gain more importance and alcohol use comes into play, the style of which influences and is influenced by the aforementioned issues.

We will first briefly summarize the literature of studies describing monofactorial relations of adult AUDs with known internal and external risk factors, review some examples and models of gene–environment-interactions influencing alcohol use, and describe how they might act already during childhood to influence later drinking and some specific associated disorders.

2. Internal and external risk factors for alcoholism, and their interaction

2.1. Internal factors: genes and permanent consequences of early experiences

One of the best known determinants of drinking refers to the observation that alcoholism runs in families (Maier, 1995; Cotton, 1979; Bierut et al., 1998). Studies with adopted twins found that more than half of this risk can be attributed to genetic factors (Prescott and Kendler, 1999; Heath et al., 1997; Sigvardsson et al., 1996; Goodwin et al., 1973). Offspring of alcohol-dependent parents (family history positive, FHP) run a four to eight-fold increased lifetime risk to develop alcoholism, compared to individuals without a family history of alcoholism (family history negative, FHN). Some authors thought that this would predominantly affect the sons, but not the daughters of alcoholics (McGue et al., 1992; Goodwin et al., 1977). More recent studies found that a marked genetic risk also affects women (Prescott et al., 1999; Pickens et al., 1991) and that the earlier negative results were due to recruitment artifacts (Prescott and Kendler, 2000). However, genes predisposing for alcoholism in women are apparently more often transferred from the mother than from the father (Bohman et al., 1981).

2.1.1. Effect of specific genes

Although there is no doubt that the risk for alcoholism is heritable, the responsible genes remain largely unknown and most researchers agree that there is a multigenic transmission. Several candidate genes were reported to be associated with alcoholism; however, the number of positive and negative studies is almost balanced for most genes. These ambiguous results are in line with the concept of a multigenic transmission,

since this implies that no single contributing gene alone can be expected to explain much of the phenotypic variance.

Only two specific genes could be identified which unambiguously influence the risk for alcoholism in humans, namely alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH). They are both involved in the regulation of alcohol metabolism and some of their polymorphisms apparently act as protective factors. For example, the allele frequency of ADH2*2 in alcohol-dependent patients is lower than in control samples without AUD (Chen et al., 1999), which is probably due to the higher metabolic activity of the resulting enzyme (Neumark et al., 2004). The influence of polymorphisms of the ALDH-gene is even better documented. The ALDH2*2-isoform codes for an enzyme with less metabolic activity, giving rise to flushing and intolerance even after drinking only small amounts of alcohol. This polymorphism is abundant in Asian populations and protects against development of alcoholism (Maezawa et al., 1995).

Other findings concerning candidate genes were recently reviewed (Dick and Foroud, 2003; Schumann et al., 2003; Kreek et al., 2004) and are much more ambiguous. These findings include the genes coding for dopamine D2-, D3-, and D4-receptors, dopamine transporter, monoamin-oxidase A, catechol-*O*-methyl-transferase, the serotonin transporter, tryptophan-hydroxylase, 5-HT 1B and 5-HT 2A receptors, GABAA-receptor, μ-opiate receptor, neuropeptide Y, cAMP, protein kinase C, protein tyrosine kinase fyn, and the glutamate transporter EAAT2.

2.1.2. Endophenotypes that are associated with the risk for alcoholism

Establishing a causal link between internal risk factors and the development of alcoholism requires long-term catamnestic studies which are difficult to perform. After decades of work, such a relation was substantiated for a positive family history of alcoholism, but the underlying mechanisms conferring the risk are still unknown. In this situation, many authors turned to studying healthy, non-addicted subjects with a high risk for later development of AUD, defined by a positive family history for alcoholism (see Newlin and Thomson, 1990 for review). The general goal of such research is to find markers of the increased risk, which might shed light on the underlying physiological mechanisms. This strategy represents the concept of an "endophenotype", i.e. a biological feature which, unlike a phenotype, is hidden to direct clinical observation, but is genetically determined and closely linked with the disease of interest. A number of such observations were described in recent years, and the ones pertaining to stress reactivity are summarized in Table 1. These findings are based on statistically significant differences between risk groups, but only explain a minor part of the observed variance. Therefore such measures do not allow for individual predictions of the risk for alcoholism. Such studies with high risk groups were performed regarding both development and maintenance of alcoholism, bearing in mind that the factors influencing relapse probably differ from those that determine initial development of the disease. Table 1 includes examples for both issues.

Recent studies focused almost exclusively on detecting risk factors for AUDs. Research on possible protective factors was neglected, although there is good reason to assume that this is an important issue. One method to study protective factors would be to investigate high risk subjects who do not develop alcoholism despite their genetic predisposition and despite being exposed to alcohol.

Table 1
Putative stress reactivity-related endophenotypes for the risk for alcoholism

Marker	Findings in FHP high risk subjects compared to FHN controls
ACTH response to CRH	Decreased ACTH stimulation (Waltman et al., 1994)
ACTH and cortisol response to opiate antagonist	Increased ACTH stimulation (Wand et al., 1998, 1999a; Hernandez-Avila et al., 2002)
Cortisol response to ACTH	Normal cortisol stimulation (Wand et al., 1999b)
Baseline cortisol and ACTH secretion	Unaltered (Wand et al., 1999b; Zimmermann et al., 2004a,b; Uhart et al., 2006; Dai et al., 2002) or decreased ACTH (Dai et al., 2002)
Unmodulated acoustic startle reflex	Decreased (Zimmermann et al., 2004c) or unaltered (Grillon et al., 1997)
Right amygdala volume	Reduced (Hill et al., 2001)
Recovery of HPA hyperactivity after withdrawal	Earlier (Zimmermann et al., 2003)

2.1.3. Permanent consequences of early adverse experiences

Adverse experiences caused by the social environment clearly are external factors as opposed to the inherited characteristics described above. However, if they occur early in life and gravely affect a child, they can cause changes that persist even after the cause is no longer present. Under certain circumstances such alterations can be effective throughout the adult lifespan, much like a scar that forms after suffering an injury. In being permanent, such changes resemble the effect of genes and are in fact acquired internal factors or "organism variables" in the language of behavior therapy.

Some examples of such permanent adaptations are relevant for development of substance use disorders including alcoholism. In rat (Huot et al., 2001) and primate experiments, intermittent maternal separation during the first few weeks of postnatal life resulted in persistently increased reactivity to social stress and increased spontaneous alcohol intake when these animals were grown-up (Fahlke et al., 2000; Higley et al., 1991). Remarkably, no difference in these animals' baseline behavior could be found compared to controls without maternal separation. In humans, the effect of such pervasive early developmental experiences can be assessed in retrospect. One study found that alcohol-dependent adolescents had more often experienced childhood abuse than non-dependent controls (Clark et al., 1997). In another study, response to experimental stress was found to be increased in adult women who were sexually abused during childhood (Heim et al., 2002).

2.2. Stress and alcohol exposure as prototypes of external risk factors

It is widely accepted that an individual's drinking behavior is influenced by his or her social environment. This applies to

social drinking and to development and maintenance of AUD in both adults and adolescents. Owing to the complexity of human social behavior, it is extremely difficult to prove causality in such relations according to scientific standards. The one single factor whose causal influence is most clearly established is environmental stress (Pohorecky, 1991), and for that reason we will focus on the various aspects of stress exposure and stress reactivity that pertain to alcoholism.

2.2.1. Influence of stress on consumption and on the pharmacologic effects of alcohol

Environmental stress is associated with increased social drinking and with worsening of AUD. The respective literature of prospective and retrospective epidemiological studies was recently reviewed by Sinha (2001) and by Brady and Sonne (1999). A central topic of these reports was exposure to work stress (Ragland et al., 2000; San Jose et al., 2000). Other daily hassles can yield a similar effect upon drinking, as can major negative life events such as breaking up personal relationships, bereavement, or unemployment (Brady and Sonne, 1999; Jose et al., 2000; Cole et al., 1990). Sex also appears to modulate how stress is associated with drinking (Cooper et al., 1992). This could not be replicated, however, in another study (Sinha, 2001).

The group of de Wit (de Wit et al., 2003) used laboratory experiments to investigate whether standardized exposure to psychosocial stress affected alcohol drinking during the subsequent recreation period. They found a minor increase in spontaneous drinking, which could not be explained by altered psychopharmacological effects of alcohol. The sedating effect of a weight-adapted dose of alcohol, however, was more prominent after the stressor than after a control task (Soderpalm and de Wit, 2002). A similar result was reported by Breslin et al. (1995), who studied the combined effects of recent negative life events and a laboratory stress test. The combination of both significantly reduced subjective intoxication after drinking 0.7 g/kg ethanol, compared to a control group which received the laboratory stressor but had not experienced recent adverse life events.

One plausible reason why de Wit et al. were unable to demonstrate stress-induced drinking is that in humans only very mild experimental stress protocols can be applied. This might explain why similarly designed animal experiments could clearly show a causal relation between increased alcohol intake and stressors such as physical constraint, foot shock, novel environment, or social defeat. This literature also was reviewed by Sinha (2001) and Brady and Sonne (1999). Other animal studies found that acute stress exposure promoted the development of acute tolerance against alcohol (Mastropaolo et al., 1992; Maier and Pohorecky, 1986; Peris and Cunningham, 1987; Nash and Maickel, 1988), which might further explain why rodents drink more when being stressed.

2.2.2. Influence of HPA system activity on drinking

Whether or not environmental stress becomes relevant to an individual does not only depend on how often a stressor occurs and how severe it is, but how strong the emotional, autonomic nervous, endocrine and behavioral responses are. The core process that actually defines a stress response is activation of the limbic-hypothalamic-pituitary (HPA) system, with cortisol as the effector hormone. When confronted with the same stressor, individuals vary greatly in their endocrine response. This can be seen after standardized physical exercise (Leal-Cerro et al., 2003; Kirschbaum et al., 1992), psychological (Dugue et al., 1993) and psychosocial stress (Kirschbaum et al., 1993), and after life-threatening accidents (Hetz et al., 1996).

One important mechanism by which stress influences drinking and the effects of ingested ethanol appears to consist in modulation of corticosteroid secretion. The evidence supporting this notion predominantly comes from animal behavioral research as reviewed by Piazza and Le Moal (1997). For example, stress-induced secretion of corticosteroids stimulates dopamine in the nucleus accumbens in a similar pattern as do drugs of abuse. Such dopaminergic activation is thought to underlie the rewarding effect of drugs (Berridge and Robinson, 1998) and therefore might be one mechanism by which glucocorticoids can promote substance use (Piazza and Le Moal, 1998).

Another line of evidence is based on experiments where animals were adrenalectomized, which blocked stress-induced sensitization to amphetamines and opiates, as well as the food restriction-induced enhancement of alcohol drinking (Hansen et al., 1995). Food restriction also reinstated cocaine seeking in intact, but not in adrenalectomized rats (Shalev et al., 2003). Moreover, the drug-sensitizing effect of experimental stressors can be mimicked by repeated corticosterone administration. The pharmacological effect of alcohol might also be modulated by corticosteroids, since voluntary drinking in rats was transiently reduced by adrenalectomy and was not only restored, but increased above baseline by administration of corticosterone (Fahlke et al., 1995). The same effect occurs in ethanol-preferring rats whose corticosterone synthesis is blocked by metyrapone (Fahlke et al., 1994). Also, intracerebroventricular administration of small corticosterone dosages could restore drinking after adrenalectomy and increase drinking in intact animals (Fahlke et al., 1996). Stress-induced secretion of glucocorticoids apparently can induce cross-sensitization to later alcohol exposure via their effect on mesolimbic dopaminergic neurons, even if there is no close connection in time (Phillips et al., 1997). Based on these findings, Piazza and Le Moal (1997) suggested that glucocorticoids per se might have rewarding properties. On the other hand, some findings by Nash and Maickel (1988) were equivocal, since hypophysectomy and chronic dexamethasone treatment, but not adrenalectomy attenuated the increase in alcohol consumption that was seen after exposure to stress that was induced by immobilization or by placement in a novel environment.

Glucocorticoid action also appears to be a prerequisite for the development of chronic tolerance following long-term alcohol administration. In rats, the increase of brain tryptophan-hydroxylase that is associated with tolerance was attenuated by adrenalectomy, as was the occurrence of audiogenic seizures during subsequent alcohol withdrawal. Both were restored by corticosterone substitution (Sze, 1977). This may be interpreted

as a "permissive" corticosterone effect on the neuroadaptive changes that are induced by alcohol exposure, as is depicted in Fig. 1.

This concept implies that the HPA system is able to modulate drinking even in the absence of stress, suggesting a more general role concerning the development of addictive disorders.

This wealth of evidence raises the question whether stress increases substance use exclusively via HPA activation, or whether there are also HPA-independent mechanisms. Indeed, Mantsch and Katz (2006) recently reported that a glucocorticoid surge is necessary but not sufficient for electric foot shock stress to increase operant cocaine self-administration. HPA-dependent and independent mechanisms conveying stress effects on substance use might converge in the concept of the extended amygdala and the role of corticotrophin-releasing hormone (CRH) therein. Extrahypothalamic CRH is thought to be critically involved in depression, anxiety and substance use disorders (Sinha, 2001; Shalev et al., 2006). In some parts of the amygdala, it is attenuated by adrenalectomy (Santibanez et al., 2005) and stimulated by glucocorticoids (Makino et al., 2002). Psychological aspects of stress exposure may also be able to directly stimulate amygdaloid CRH (Makino et al., 2002). This might help to explain why recent studies found that reinstatement of alcohol- or heroin-seeking behavior by various stressors critically depended on activation of CRH, but not on glucocorticoids (Le et al., 2000; Shalev et al., 2006).

2.2.3. Influence of drinking on stress reactivity

The interaction between stress and drinking is not unilateral with the former promoting the latter, but the pharmacological alcohol actions also influence how a stressor is experienced and consecutively can modify physical and emotional stress responses. Alcohol-induced stress response dampening is thought to be a central mechanism promoting the development of alcoholism. This was first expressed in Conger's tension reduction hypothesis (Conger, 1956), which posits that the pharmacologically sedating effects of alcohol are deliberately used to alleviate unpleasant feelings of inner tension that are brought about by recent stress exposure. If such an effect is repeatedly experienced, this behavior can develop into a habit and permanently link stress to drinking.

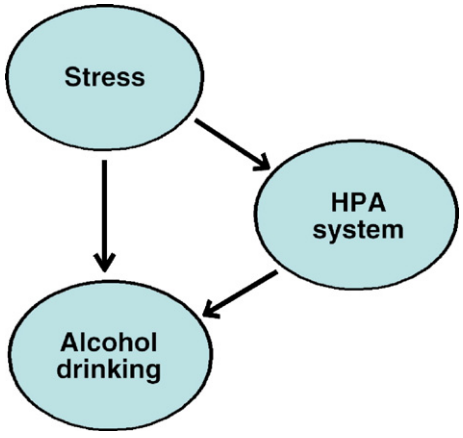

Fig. 1. Permissive effect of HPA system activation on drinking. Note that corticosteroids may substitute for stress to promote drinking.

This hypothesis is supported by a series of studies. Some of them suggested specific prerequisites for an alcohol effect to take place, such as involvement of a cognitive task or the timing of drinking, individual differences, and situational factors (Sayette, 1999; Young et al., 1990; Steele and Josephs, 1988; Curtin et al., 1998). Laboratory experiments confirmed that alcohol attenuates physiological reactivity and anxiety in response to stressors, which could not be explained by expectancies of a psychotropic alcohol effect (Levenson et al., 1980; Sher and Walitzer, 1986; Eisenhofer et al., 1986). In patients with panic disorder, alcohol reduces subjective anxiety and the probability of panic attacks upon experimental provocation (Kushner et al., 1996). These alcohol effects are not due to a general dampening of central nervous functioning, but seem to be caused by specific effects on higher brain functions such as cognitive performance and associative memory (Stritzke et al., 1996).

Based on these insights, Sayette (1993) formulated a more sophisticated "appraisal disruption hypothesis", suggesting that alcohol dampens a stress response only if it is consumed prior to stress exposure. In that case, alcohol would interfere with memory recall, hindering comparison of relevant memories with the imminent situation, and thus impede forming a cognitive assessment and emotional appraisal of the situation as being unpleasant. Consequently, the stress situation would cause less anxiety. This model could be confirmed in one study that was specifically designed to test the hypothesis (Sayette et al., 2001).

More indirect experimental evidence for alcohol-induced appraisal disruption comes from recent results of our laboratory: after repeated exposure to a psychosocial stress paradigm, the cortisol response remained suppressed during the second test if the subjects had undergone the same procedure one week before at a blood alcohol level of approximately 50 mg% (=0.5‰) (Zimmermann et al., 2004a). Our interpretation is that alcohol might have interfered with appraising the situation, making it less aversive and attenuating learning of negative associations. Therefore, the memories recalled upon re-exposure to the situation might have been less unpleasant, which would result in less emotional distress and a smaller stress response.

2.3. Gene–environment-interactions

For a long time, geneticists, psychologists, and social scientists tried to explain addictive disorders exclusively with insights from their own field of expertise. Only recently evolved the idea that it is not the known internal and environmental factors per se which are crucial for the development of addictive disorders, but rather their mutual interaction. This concept applies to virtually all psychiatric and physical diseases with a genetic component. With respect to addictive disorders, it can be enhanced by including some acquired internal factors in addition to genes (e.g., childhood trauma), and by considering gene–gene and environment–environment-interactions (e.g., stress with alcohol exposure).

2.3.1. Simple interactions between specific genes and stress

In a recent paper on the interaction between the serotonergic system and stress, Caspi et al. (2003) presented evidence showing that negative life events triggered depressive disorders almost exclusively in carriers of at least one short allele of the serotonin transporter gene. This polymorphism of the 5-hydroxy-tryptophan-gene-linked polymorph region is functionally relevant, since the short version is associated with reduced transcription and less activity of the serotonin transporter, resulting in more and longer lasting serotonin activity in the synaptic cleft (Lesch et al., 1996). Another implication is that this polymorphism might be linked with an increased risk for alcoholism, although the respective findings are far from being consistent (Feinn et al., 2005; Kweon et al., 2005).

Other interactions of this polymorphism with environmental stimuli were reported by Heinz et al. (2005), who used functional MRI to show that healthy carriers of a short allele had more activation of both amygdalae upon presentation of aversive visual stimuli compared to homozygous carriers of the long allele. This can be thought to indicate more intense emotional reactivity. A similar observation was made concerning the Val158Met-polymorphism of the catechol-*O*-methyl-transferase gene. Following presentation of aversive slides, the activity in limbic and connected prefrontal brain areas was significantly enhanced in carriers of at least one met-allele compared to homozygous val-alleles. This was interpreted to signify reduced emotional stability in reaction to aversive environmental stimuli (Smolka et al., 2005). Both findings hint to increased stress reactivity. In val-carriers who are also susceptible for alcoholism, this might result in more alcohol use in order to control stress-associated negative emotions.

Concerning the dopamine DRD2 receptor Taq1 polymorphism, there are two studies suggesting gene–stress interactions. In alcohol-dependent carriers of the A1 allele a positive correlation between addiction severity and stress due to negative life events during the last 12 months was reported (Bau et al., 2000). Madrid et al. (2001) found a positive correlation between scores on a work stress questionnaire and the Michigan Alcoholism Screening Test results in carriers of at least one A1 allele, but not in subjects homozygous for the A2 allele.

2.3.2. Simple interactions between genetic risk and alcohol exposure

Despite the accumulating evidence for associations between alcohol dependence and genetic polymorphisms, little is known about whether genes might also modify the alcohol effects a subject experiences after drinking. On the other hand, it is long known that offspring of alcoholics react differently to alcohol intake, compared to FHN controls. The respective literature on family history effects was reviewed by Newlin and Thomson (1990), and an update is given in Table 2.

For example, Schuckit et al. found that sons of alcoholics responded less to alcohol administration. This was true for measures such as HPA activity (Schuckit et al., 1988, 1987b), prolactin (Schuckit et al., 1987a, 1983), body sway (Schuckit, 1994), subjective intoxication (Schuckit, 1984), or combinations of theses parameters (Schuckit and Gold, 1988). Meanwhile, these findings were partly confirmed in daughters of alcoholics (Schuckit et al., 2000). Some of these markers predicted later development of alcoholism even in the absence of a positive family history (Schuckit, 1994; Schuckit and Smith, 1996), which suggests that their frequent presence in FHP subjects might represent one mechanism by which the effect of genes translates into risk.

Other examples of a reduced response to alcohol-related stimuli include the observation that FHP alcoholics show less HPA disturbance following alcohol withdrawal (Zimmermann et al., 2003). Healthy FHP subjects who were administered ketamine to stimulate their NMDA receptor system showed less psychopathological signs of intoxication, which might be one explanation why they also respond less to alcohol (Petrakis et al., 2004). On the other hand, some authors observed increased alcohol effects in FHP compared to FHN subjects (see Table 2).

Table 2
Gene–environment-interactions regarding altered response to alcohol administration in healthy, non-dependent FHP high risk subjects compared to FHN controls

Parameter	Alcohol effect in FHP subjects compared to FHN controls		
	Decreased	Unaltered	Increased
Subjective intoxication	(Schuckit and Gold, 1988; Schuckit et al., 2000)		(McCaul et al., 1991b; Nagoshi and Wilson, 1987; McCaul et al., 1991a)
Body sway	(Schuckit, 1994; Schuckit and Gold, 1988)	(Schuckit et al., 2000)	(McCaul et al., 1991b)
Prolactin stimulation	(Schuckit et al., 1987a, 1983)		
Baseline HPA activity	(Schuckit et al., 1988, 1987b; Dai et al., 2002) (ACTH)	(Zimmermann et al., 2004a; Dai et al., 2002 (cortisol))	
Corticotropin response to oCRF stimulation	(Waltman et al., 1994)		
β-endorphin stimulation			(Gianoulakis et al., 1996)
Heart rate increase			(Conrod et al., 1997; Peterson et al., 1996)
EEG alpha frequency band response			(Volavka et al., 1996)
Attenuation of acoustic startle reflex	(Grillon et al., 2000)	(Zimmermann et al., 2004c)	
Cognitive impairment	(Erblich and Earleywine, 1999)		
Acute tolerance to alcohol	(Blekher et al., 2002; Morzorati et al., 2002; Ramchandani et al., 1999)	(Nagoshi and Wilson, 1987)	

Family history determines not only acute alcohol effects, but also how the brain adapts to the presence of alcohol, i.e., alcohol tolerance. Tolerance has different aspects, which develop within minutes to weeks. For example, acute tolerance occurs within a single drinking session (Radlow, 1994; Martin and Moss, 1993). The group of O'Connor found that such neuroadaptive processes are more prominent in offspring of alcoholics, as measured by changes in subjective intoxication (Ramchandani et al., 1999; Morzorati et al., 2002) and in saccadic eye movements (Blekher et al., 2002). In earlier studies, however, Nagoshi and Wilson (1987) did not find such an effect. Acute alcohol tolerance may play an important role in the development of alcoholism, since marked tolerance results in increased exposure. This association was assumed by Newlin and Thomson (1990) to be an important mechanism by which genes increase the risk for alcoholism. Still, thorough experimental validation of this concept is missing.

2.3.3. Interactions between genetic risk, stress, and experimental alcohol exposure

There are a number of reports supporting the hypothesis that offspring of alcoholics experience more stress response dampening after drinking alcohol, which might be another crucial reason why they are at risk. This assumption is based on the tension reduction hypothesis (Conger, 1956) and is supported by earlier findings in FHP subjects who were exposed to stressors such as aversive electrical stimuli, mental arithmetics, or public speaking tasks. If administered prior to the stressor, alcohol dampened the response more in FHP than FHN subjects, as measured by heart rate, finger pulse amplitude, pulse transit time, or by subjective stress ratings (Sher and Levenson, 1982; Levenson et al., 1987; Finn and Pihl, 1988, 1987; Finn et al., 1990, 1992; Harden and Pihl, 1995; Steward et al., 1992; Conrod et al., 1998; Sinha et al., 1998). All those studies, however, did not measure HPA system stimulation, which is widely agreed to be the core parameter signifying a stress response. They were also performed in adults above the United States legal drinking age, who responded to public announcements of the study.

In an attempt to characterize mechanisms contributing to the initial development of AUD in adolescents, we performed a laboratory study comparing a sample of healthy, non-dependent early adult sons of alcoholic fathers with FHN males. This sample was recruited from a representative population survey whose participants were randomly selected from a municipal registry. This method avoids any selection bias during recruitment. Since alcohol cannot be given to minors, all participants had to be past the legal drinking age in Germany, i.e., 18 years. The mean and SD age was 20.2±2.5 years, with 75% aged between 18 and 21 years. Two experiments involving psychosocial stress and induction of anxiety-related affective states were performed with this sample and are described below.

2.3.3.1. Family history, alcohol, and public speaking stress. In the light of the above described findings on the involvement of the HPA system in alcoholism, there is good reason to assume that the link between stress and drinking might actually consist in activation of the HPA system. Therefore we investigated how alcohol modifies HPA reactivity to a standardized laboratory stressor, and whether this effect depends on the genetic risk for alcoholism.

For the first experiment we used the Trier Social Stress Test, which is a standardized laboratory stressor that was validated in the context of various external conditions (Kirschbaum et al., 1992, 1993, 1994, 1995, 1997, 1999). Confirming our hypotheses, we found that the high risk FHP subjects responded with more stress-induced corticotrophin and cortisol secretion compared to FHN controls. Their stronger stress response was attenuated by prior drinking of 0.6 g/kg alcohol, whereas in FHN subjects no alcohol stress response dampening occurred. Consequently, the stress response did not differ between risk groups in experiments involving alcohol drinking (Zimmermann et al., 2004a). The same effect was noted for vasopressin (AVP) secretion, which together with CRH stimulates corticotrophin. Stress-induced AVP secretion was increased in FHP subjects, but normalized by prior alcohol drinking (Zimmermann et al., 2004b).

2.3.3.2. Family history, alcohol, and induction of anxiety-related affective states. The second mechanism that was tested in the same subjects relates to the relaxing and anxiolytic properties of alcohol. The above described literature suggests that these effects might be more prominent in the sons of alcoholics compared to FHN controls. In recent years, registration of the acoustic startle reflex has been found to be a sensitive tool enabling to demonstrate subtle changes of anxiety and affective states (Filion et al., 1998; Davis et al., 1993). The startle reflex can be modified by fear potentiation and emotional modulation. Fear is induced by threat of aversive electrical shocks (Grillon et al., 1993a,b) and visual stimuli standardized for their emotional valence can be presented to induce positive or negative emotional states (Lang et al., 1990; Hamm et al., 1997). Earlier studies found that negative emotional slides increased the startle reflex in FHN controls, but not in FHP high risk subjects (Miranda et al., 2002). Alcohol administration dampened the baseline startle reflex level, but less so in FHP than FHN subjects (Grillon et al., 2000)

We used this method to study passive avoidance anxiety induced by announcing aversive electric shocks and emotional modulation (International Affective Picture System, Lang et al., 1988), with and without prior alcohol administration in the same subjects as described above. The baseline startle reflex level prior to drinking was significantly lower in the FHP participants. Their response to electric shock announcement and to the emotional slides, however, was not different from FHN controls. Also, all alcohol effects on baseline and modulated startle reflex were the same in both risk groups (Zimmermann et al., 2004c).

When interpreting the above described effects of a positive family history, one must bear in mind that they may not all be exclusively caused by genetic influences. Rather, problematic parental behaviors associated with drinking may contribute to their children's increased risk, either by producing the early adverse experiences described in Section 2.1.3., or by inappropriate education concerning alcohol use.

3. Childhood behavior disorders as early risk factors for alcoholism

Among the most prominent individual risk factors for AUD are behavior disorders usually emerging during childhood and adolescence. They are specified into three diagnoses by DSM-IV (American Psychiatric Association, 1994) as follows:

1 Attention deficit/ hyperactivity disorder (ADHD), characterized by symptoms of inattention, impulsivity and hyperactivity.
2 Oppositional defiant disorder (ODD) with temper tantrums, disobedience, blaming others for ones behavior, defying rules, being annoyed easily, deliberately annoying others, and frequent display of anger, spitefulness or vindictiveness (diagnosed, if 4 out of these symptoms are present for at least 6 months).
3 Conduct disorder (CD), displaying symptoms of antisocial behavior and serious rule violations like aggression toward people and animals, deceitfulness, theft, destruction of property and frequent truancy.

ICD-10 refers to conceptually similar, but not equivalent disorders: hyperkinetic disorders (F90) with the subgroup of hyperkinetic conduct disorder (F90.1) and conduct disorder (F.91) comprising the diagnosis of oppositional defiant disorder (F91.3) (World Health Organization, 1993; see also Rowe et al., 2005). ADHD and ODD/CD are very common: ADHD occurs in childhood with a prevalence of 6% to 12%; boys are far more frequently affected than girls (Biederman and Faraone, 2005). Meta-analyses suggest prevalence rates for ADHD from 0.2 to 20%; in ODD and CD they can range from 1.2% to 15% and 1% to 17%, respectively (Costello et al., 2005).

ADHD and ODD/CD are highly comorbid. In a recent longitudinal study, Biederman et al. (2006) demonstrated in ADHD children a six-fold elevated risk to develop ODD, CD or antisocial personality disorder (ASPD) and a two-fold risk for any substance dependence within the subsequent 10 years, compared to non-ADHD controls. CD beginning in early childhood, i.e., before age 10, very often persists into adolescence and adulthood and is then called life-course persistent type. It can be distinguished from an episodic type that only emerges in adolescence and fades by early adulthood (Moffitt, 1993). Individuals with the life-course persistent type are more likely to develop ASPD later and report more alcohol related problems compared to those with episodic type CD. However, compared to the general population, the life-course persistent as well as the episodic types of CD have higher rates of alcohol related problems (Moffitt et al., 2002).

3.1. Childhood behavior disorders and alcohol use

3.1.1. Parental alcohol use and childhood behavior disorders

There are multiple associations between behavior disorders in childhood and alcohol related problems: children of alcoholics are at elevated risk to develop ADHD (Knopik et al., 2005) and ODD or CD (Barnow et al., 2002; Furtado et al., 2002), and this again is a risk factor for the development of harmful alcohol and other substance use patterns (Clark et al., 1999; Gittelman et al., 1985). Maternal alcohol drinking during pregnancy can result not only in fetal alcohol syndrome, but puts children also at a higher risk for CD (Schonfeld et al., 2005) and ADHD (Knopik et al., 2006).

3.1.2. Childhood disruptive disorders and later alcohol use disorders

In prospective longitudinal studies the association between ODD/CD symptoms and AUD could be established in non-clinical samples. Caspi et al. (1996) showed that 3-year-olds with a lack of behavioral control were about twice as likely to have a diagnosis of alcohol dependence at age 21, compared to children of the control group. If only the boys were examined, the hazard ratio of alcohol dependence at age 21 was 2.7 (Caspi et al., 1996). Molina and Pelham (2003) reported in their longitudinal study that ADHD in childhood is associated with a higher rate of intoxications and more alcohol related problems, compared to unaffected children and adolescents. An analysis of subgroups revealed that persistence of ADHD into adulthood and development of a comorbid CD were the best predictors for symptoms of alcohol dependence and intoxication (Molina and Pelham, 2003).

Not only is ODD/CD associated with heavy drinking, but also the other way round, i.e., adolescents with alcohol problems develop ODD/CD symptoms secondary to their alcohol use. This was demonstrated by Brown et al. (1996), who reported that in a group of 166 16-year-olds assigned for treatment of alcohol and drug abuse, 95% had shown CD-type behavior in the past, but only 47% fulfilled criteria of CD if behaviors related to alcohol and drug use were disregarded. This group also had a higher proportion of fathers with ASPD and a worse prognosis for alcohol treatment outcome 2 years later.

3.1.3. Childhood ADHD and later alcohol use disorders

While the risk of alcohol abuse and dependence is elevated in adolescents with comorbid ADHD and CD (Clark et al., 2002; Smith et al., 2002), the impact of mere ADHD on AUD remains uncertain. The high comorbidity rate of these disorders complicates analyzing this association, since groups with ADHD without comorbidity tend to be very small and have low statistical power. In the study mentioned above, Molina and Pelham (2003) found a 2.4-fold elevated risk for at least one symptom of AUD in ADHD children without comorbid CD. The Mannuzza group, however, could not always find associations between ADHD persisting from childhood into adolescence, and later AUD (Mannuzza et al., 1998). There is one study showing that despite the 4 to 5-fold elevated risk of children with treated ADHD to develop later CD or ASPD, and despite their 7-fold elevated risk to suffer from nonalcohol substance use disorders, the risk for AUD was not elevated (Mannuzza et al., 1991).

3.1.4. Explanations for the link between disruptive behavior and alcohol use disorders

There are two possibilities to explain the high comorbidity of ADHD and ODD/CD with AUD: since these disorders usually emerge in childhood and early adolescence, i.e., before the

development of AUDs, they might be either a causal risk factor or a mere indicator of an underlying disposition for AUDs. The nature of these associations would be essential for treatment: in case of a causal association, effective treatment of disruptive disorders should reduce the risk for AUDs or alcohol related problems. If they were only indicating a higher vulnerability for AUDs, early alcohol prevention programs, focused on this high risk group would be more appropriate.

There is some evidence for the first possibility. Biederman et al. (1999) compared alcohol abuse and dependence in treated vs. non-treated ADHD patients with non-ADHD controls. The non-treated group had a 5.8-fold higher risk of developing AUDs compared to non-ADHD controls (95% CI: 1.7–19.3), while the medicated group had only about 16% of the risk for AUDs compared to the unmedicated group (OR 0.16; 95% CI: 0.05–0.57). This means that their risk was similar to the non-ADHD controls. Katusic et al. (2005) found less clear but same-directional effects in boys but not in girls, since the OR for substance abuse in medicated vs. non-medicated ADHD boys was 0.5 (95% CI: 0.3–0.9). However, other studies of Biederman et al. (2006) showed, that even in a sample of mostly (93%) treated ADHD patients, the rate of SUDs at 10-year follow up was significantly higher than in controls, which is in line with the results that Gittelman et al. (1985) found in their sample of drug-treated ADHD boys.

The results of Mannuzza et al. (1991) can shed some more light into these associations. In the first study (Gittelman et al., 1985), children were mostly treated with medication only and still did have an increased risk for later AUD. The second study (Mannuzza et al., 1991), involved participants who were predominantly treated with medication and/or behavioral therapy. Here, no elevated risk for AUDs, compared to controls could be found. Possibly, the psychotherapeutic intervention gave participants of the treatment group new competences, protecting them from development of comorbid AUDs though not from progress into other disruptive disorders.

3.2. Common genetic vulnerability in childhood behavior disorders and alcoholism

3.2.1. Familial heritability

Family, twin and adoption studies have provided much evidence for the impact of genetic factors in ADHD and ODD/CD (Faraone and Doyle, 2001; Rhee and Waldman, 2002). The heritability estimates of ADHD vary from 61% to 99% (Faraone et al., 2005), making it one of the most heritable disorders in childhood and adolescence. Parental antisocial behavior and ASPD predict preadolescent development of CD in sons and a less favorable course of the disorder (Brown et al., 1996). The impact of genetic factors in ODD/CD seems to vary by age and by the kind of behavior problems. While in children the phenotypic variation is determined by common genetic as well as by shared environmental factors (Edelbrock et al., 1995), it appears to be predominantly genetic factors that contribute to ODD/CD in late adolescence and adulthood (Jacobson et al., 2002). This might be due to different behavior problems by which ODD/CD in different ages is characterized: Edelbrock et al. (1995) reported that aggressive behavior in childhood is predicted by genetic factors, while delinquent behavior at this age is associated with shared environmental factors. Therefore the heritability of childhood aggressive behavior appears to be higher than that of delinquent behavior. Supporting this hypothesis, Tuvblad et al. (2005) recently demonstrated that in girls the development from childhood delinquent and aggressive behavior to adolescent delinquency was influenced by genetic factors, while in boys environmental factors accounted for the course from delinquent behavior to delinquency. On the other hand, Jacobson et al. (2002) did not find sex-specific genetic influences in the development of ODD/CD.

ADHD, ODD symptoms and alcohol/substance related problems might all trace back to one single underlying factor. Krueger et al. (2002) presented a model with a latent factor of disinhibition or "externalizing" behavior, fitting best to their data of 1048 17-year-old participants from the Minnesota Twin Family Study. This "externalizing" factor was highly determined by additive genetic effects (load: .90), was independent from shared environmental effects (.0) and moderately associated with non-shared environmental factors (.43). The "externalizing" factor itself showed high associations to adolescent antisocial behavior (.78), conduct disorder (.58) and alcohol dependence (.71). In summary, these data suggest that the reason for the high comorbidity of alcoholism and adolescent behavior disorders lies in this broad latent factor.

3.2.2. Candidate genes

Linkage and association studies suggested a variety of candidate genes for ADHD and ODD/CD, which were recently reviewed by Faraone et al. (2005) and Comings et al. (2000). In particular, aggressive behavior and CD were found to be associated with genetic variations in the serotonin (5HT) system (Lesch and Merschdorf, 2000). Not surprisingly, given the high comorbidity and heritability of AUD and ADHD/ODD/CD, many of these candidate genes are also relevant in the transmission of AUD. These overlapping genes include most of the catecholaminergic genes, i.e. those coding for the dopamine transporter and the dopamine D2-, D3- and D4-receptors. They are also associated with smoking and the temperament characteristic of novelty seeking (Laucht et al., 2005), which in turn is associated with heavy alcohol use in adolescence (Laucht et al., in press). Genetic variation in monoamine-oxidase A is not only associated with ADHD (Faraone et al., 2005) and alcoholism, but also with stress reactivity, as mentioned earlier. Other genes involved in both AUDs and ADHD/ODD/CD are related to the serotonergic system. Functional effects of the serotonin transporter alleles are well studied, with results including connections with ADHD and antisocial behavior (Faraone et al., 2005), level of response to alcohol (Hinckers et al., 2006), and gene–environment-interactions resulting in depression (Lesch, 2004).

3.3. Role of stress and childhood behavior disorders

3.3.1. Stress exposure in children with behavior disorders

Many studies demonstrated that not only alcoholism, but also ADHD and ODD/CD accumulate in an environment of

family adversity, childhood maltreatment, childhood abuse and neglect. "Family adversity" comprises of factors such as severe marital discord, low educational level of the parents, large family size, paternal criminality, maternal mental disorder and foster-care placement. Each one per se has only little effect, but when they occur in combination they can markedly increase the risk for behavior disorders (Biederman et al., 2002; Counts et al., 2005). All these influencing factors do not act in isolation, but interact with each other and with the genetic predisposition for behavior disorders. Recently, Jaffee et al. (2005) documented a strong interaction effect of childhood maltreatment and genetic disposition in the development of conduct problems. In children with a low genetic risk, the risk for developing CD increased by 2% upon exposure to maltreatment, while a high genetic risk was associated with a 24% increase of this risk in maltreatment vs. non-maltreatment groups. Stressful life events are one of the most reliable factors predicting externalizing behavior (Mathijssen et al., 1999). It is obvious that in families with parental substance use disorders or ASPD, the probability of encountering stressful life events such as low socioeconomic status, marital discord, childhood abuse, or neglect is much higher than in families without parental SUDs. On the other hand, positive parenting styles can act as a protective factor, but are much less prevalent in these high risk families. This raises the possibility that not only the presence of risk factors, but also the absence of protective factors puts these children at a higher risk for disruptive behaviors, which in turn can be a target for intervention.

3.3.2. Stress response in children with behavior disorders

Both ADHD and ODD/CD are associated with abnormalities in the endocrine system as well as in the hormonal response to stress. Most studies on variables of the hypothalamic-pituitary-adrenal (HPA) system activity were performed in boys with ODD/CD, probably because of the lower rate of these disorders in girls and the multiple endocrine factors influencing cortisol in girls. The predominant finding was that in response to stress, cortisol secretion was lower in ODD/CD compared to healthy controls (Snoek et al., 2004; Van Goozen et al., 2000), while their baseline cortisol was normal (Snoek et al., 2004; Van Goozen et al., 2000) or lower (Kariyawasam et al., 2002), and was negatively related to symptoms of CD (Oosterlaan et al., 2005; Vanyukov et al., 1993). Two studies reported conflicting results, i.e. higher baseline cortisol in CD boys at age 13 compared to controls without CD. This difference was particularly remarkable in boys with an aggressive form of CD (van Bokhoven et al., 2005). In another large laboratory study, stress-induced salivary cortisol in 16-year old males was positively related to conduct problems throughout ages 7–17 (McBurnett et al., 2005). Both baseline and stress-induced cortisol levels were negatively associated with the outcome after a therapeutic intervention for disruptive behavior disorder, i.e., patients with higher cortisol had less behavioral problems after the treatment program (van de Wiel et al., 2004).

That high cortisol is associated with better treatment outcome appears also to be true for ADHD (King et al., 1998). Lower stress response, however, might be specific for ODD/CD but not ADHD, since one study comparing adolescents with a pattern of combined ODD and attention deficit/ODD symptoms found lower cortisol response than in pure ADHD (Snoek et al., 2004).

When interpreting the stress response findings in ODD/CD it is important to bear in mind that a high percentage of these adolescents will later develop ASPD. One consistent finding in ASPD is that reactivity to external emotional stimuli is markedly reduced, which also implies low HPA activity (Virkkunen, 1985). This means that low cortisol response in ODD/CD might in fact be due to antisocial personality traits. This notion is supported by a study reporting that cortisol decreased after stress in ODD boys only if they scored low in anxiousness, while highly anxious ODD boys had a marked cortisol increase (Van Goozen et al., 1998). In other studies, low cortisol levels were more clearly related to aggressive than to non-aggressive symptoms in CD children (Oosterlaan et al., 2005), and were explained by aggressive delinquency scores in sons of psychoactive substance abusing fathers (Moss et al., 1995). Moreover, baseline saliva cortisol in preadolescent boys was not only negatively related to their CD symptoms, but also to ASPD in their fathers (Vanyukov et al., 1993), suggesting that the biological predisposition for ASPD is associated with low HPA activity in boys before they develop ASPD themselves.

The question of increased or decreased HPA response to stress was also addressed by Haller et al. (2005), who proposed to differentiate between aggressiveness driven by hyperarousal vs. hypoarousal. The latter is usually found in ASPD and in children with conduct disorder. Hyperarousal-driven aggressiveness was associated with increased stress response, but hypoarousal-driven aggressiveness with the opposite. These authors propose that low levels of glucocorticoids in ASPD are aversive and thus might be causally related to aggressiveness.

The equivocal results of behavior disorders and ASPD being associated to low levels of glucocorticoids but to a high risk for AUDs raise the question whether the risk of development of AUDs varies with HPA-axis activity. As described earlier, glucocorticoids in a certain range might have rewarding qualities (Piazza and Le Moal, 1997). It is not clear whether adolescents with ODD/CD might compensate a lack of glucocorticoids by drinking alcohol, or whether they might drink in order to reduce an elevated cortisol stress response.

4. Implications for risk reduction in adolescents

Can the risk for alcoholism be moderated in adolescents? A broad array of prevention strategies is based on the assumption that it can. Existing programs involve legislation, community (Holder, 2005) and school-based interventions, and targeted interventions in adolescents with obvious alcohol abuse (Saunders et al., 2004). Based on the above reviewed neurobiological findings, we suggest the case for preventive efforts to take place even before the first drink.

We know from adult alcohol-dependent patients that genetic risk, environmental stress, HPA system activity and alcohol exposure mutually interact over time to influence development and maintenance of addiction. "Mutually" means that the causal

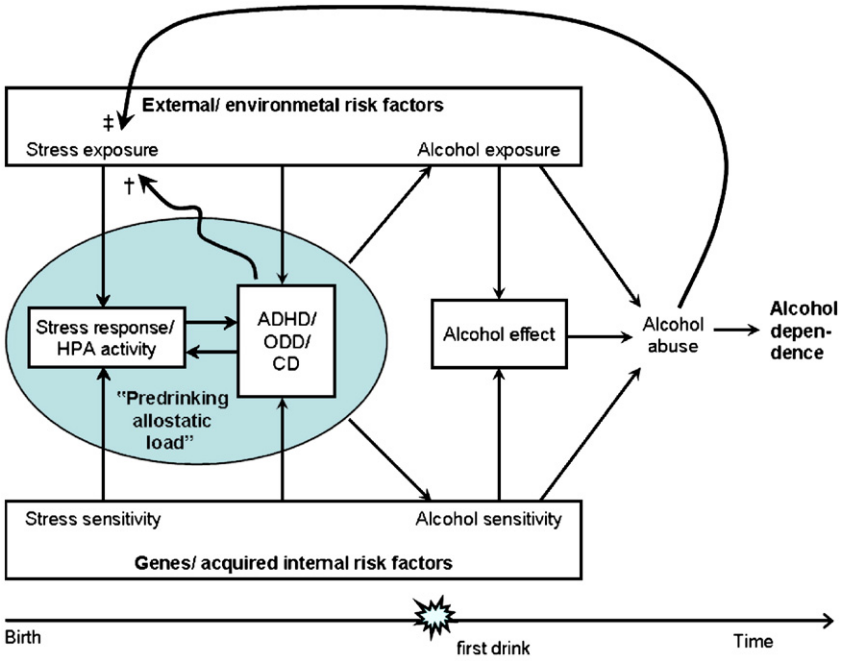

Fig. 2. Proposed model of a gene–environment-interaction process generating predrinking allostatic load in children and adolescents, which later promotes alcohol effects on the individual. ADHD = attention deficit/hyperactivity disorder; ODD = oppositional defiant disorder; CD = conduct disorder. Note two positive feedback loops since ADHD, ODD and CD† as well as alcohol effects‡ can cause increased stress exposure.

relation between some of these factors is reciprocal, and may involve positive feedback loops. For example, stress promotes drinking and drinking can cause stress. Similarly, cortisol facilitates alcohol intake and alcohol disorganizes the HPA system. To exert an effect, these loops need to be processed over and over again for prolonged periods of time, forming a process that is part of the concept of allostasis (McEwen, 2003) which is thought to be particularly important in alcoholism (Valdez and Koob, 2004).

4.1. Disruptive disorders and predrinking allostatic load in children and adolescents

Environmental stress affects not only adults but, sadly enough, can also befall adolescents, children and even newborns. This means that gene–environment interactions of exposure to and sensitivity against stress may be in effect already years before an individual has the first alcoholic drink. If stressors such as neglect or abuse start very early, i.e., within the first years of life, they even can increase sensitivity to subsequent stress. As described above, disruptive disorders are also linked to early stress exposure and are strongly associated with later alcohol problems. It is not known whether this relation is causal or simply indicates some genetic or other underlying risk factor that is shared between disruptive and alcohol-related disorders. Applying the concept of interactions between genes, environment, and behavior, the presence of a disruptive disorder must be assumed to increase allostatic load as depicted in Fig. 2. Disruptive disorders persistently perturb interpersonal relations within and beyond the family, giving rise to frequent arguments, fights, and punishment. These confrontations clearly are unpleasant and stressful experiences. Feeding back to the child, the ensuing high level of stress exposure can worsen severity of the disruptive disorder and change the sensitivity of HPA-axis to stress.

Over time this may form a vicious circle producing and increasing allostatic load. For that reason we assume that by increasing stress exposure, the presence of a disruptive disorder can actually contribute to the later development of AUD. Some consequences regarding prevention are described in Table 3.

4.2. Interactions between allostatic load and drinking

What happens if an adolescent eventually starts drinking after having undergone enough stress exposure to develop substantial allostatic load? Corresponding to the above described findings in adults and in experimental animals, one would clearly expect that high childhood stress exposure is associated with increased adolescent drinking. This is indirectly supported by one study reporting that alcohol-dependent adolescents had more often experienced stress in the form of childhood abuse compared to non-dependent controls (Clark

Table 3
Strategies to prevent adolescent alcohol use disorders that are delineated from the here reviewed data

- Identify at-risk children based on genetic, familial or behavioral risk factors.
- Offer age-specific preventive actions as early as possible (before initiation of alcohol use).
- Support pre-school children and their families to reduce early developmental stress exposure.
- Offer school children programs to learn appropriate coping with stress and aggressiveness.
- Treat attention deficit/hyperactivity disorder, conduct disorder, and oppositional defiant disorder as soon as they become apparent.

et al., 1997). Also, the above reviewed literature on early maternal separation stress suggests that the ensuing increased HPA system reactivity during adulthood is correlated with increased drinking in separated animals. The cited animal work further suggests that corticosteroids per se can increase alcohol intake.

Depending on the drinking pattern, alcohol can in turn cause stress. Reasons why this is particularly true in adolescents include their typical binge drinking style, resulting in disinhibited behaviors driven by intoxication. These often result in conflict with the law, parents, and peers, or in troublesome consequences of risky actions such as accidents, pregnancy, or injuries after fights. More regular drinking patterns can result in alcohol-induced disorders of mood or sleep, or in physical disease. Such consequences of drinking increase stress exposure which in predisposed individuals can promote more drinking.

The bulk of studies investigating social and behavioral risk factors or predictors of adolescent drinking did not evaluate the concomitant stress response as a possible underlying mechanism that might promote drinking. Studies looking at ADHD and disruptive behavior disorders found that these disorders were associated with early age at first drink (McGue et al., 2001; Kuperman et al., 2005) which in turn is a predictor of later AUD (Kuperman et al., 2001). Externalizing symptoms also are more prominent in trajectory groups of early-heavy binge drinkers (Chassin et al., 2002; Hill et al., 2000). Both findings suggest that adolescents with ADHD/ODD/CD display a particularly harmful drinking pattern early in life, explaining their increased risk for later development of alcoholism.

It is not entirely clear whether or not the above emphasized issue of stress reactivity is important for the association of ADHD, ODD and CD with AUDs, due to the ambiguous results concerning cortisol levels. Apparently, baseline and stress-induced cortisol is low in a substantial part of ODD/CD patients, which possibly represents a biological marker for later development of antisocial personality disorder. Although the physiological reactivity to stressful and other environmental stimuli is generally low in ASPD, this disorder is strongly linked with alcohol and substance use disorders. Therefore, different pathways appear to be effective in the development of addictive disorders, some of them being linked to high stress response and others not.

5. Summary and conclusions regarding prevention

Based on the here reviewed insights on gene–stress–alcohol interactions in adults, we propose to view them as a process over time which already pertains to children and adolescents, in the worst case starting at or shortly after birth. Environmental stressors and inherited stress sensitivity together determine the impact of stress on the young individual, which may lead to behavioral changes that in turn can cause more stress. In predisposed subjects, such a positive feedback loop may generate substantial predrinking allostatic load by the time they reach adolescence, which is not a good starting point for learning appropriate use of alcohol. Childhood behavioral disorders like ADHD, ODD, and CD can enforce this process, which may be one reason why they are closely associated with alcohol and substance use disorders.

In conclusion, interventions to prevent adolescent alcohol and substance use disorders should start as early as ever possible and be adjusted to age-specific requirements and opportunities. To achieve that, children at-risk need to be identified e.g. based on family history, family adversity (Rutter, 1999), and abnormal child behavior. We suggest that targeted interventions are helpful even during the first years of life, when children with the highest genetic predisposition for alcoholism very often suffer the most severe stress exposure. Actively helping children who live in at-risk families is not a new idea, but is supported by the here reviewed neurobiological facts. ADHD, ODD, and CD develop in school children and should also be actively cared for in order to moderate the risk for later AUD. School may also offer the opportunity to pick out and train at-risk children in coping with stress situations that are unavoidable for them. For example, Clark et al. (2002) reports promising first results of a treatment program involving social and problem-solving skills training for children in order to reduce their antisocial behavior. The first evaluation revealed that, compared to controls, fewer of the treated children drank alcohol, used marihuana, or had been arrested.

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