Cerebellar Lingula Thickness as a Novel Risk Factor for Alcohol and Drug Abuse

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The identification of developmental risk factors for alcoholism and drug abuse is a matter of intense research. Human twin and adoption studies have shown that alcohol intake is a highly heritable trait [1, 2]. Also, large-sample studies of alcoholism have documented moderately strong genetic contributions to variation in alcohol dependence, typically accounting for 40% to 60% of variation in risk [3]. The genetic background interacts with environmental events to produce risk for substance abuse [4]. A classic example is the individual with a low level of response to alcohol. Indeed, subjects who require greater amounts of alcohol to exhibit balance deficits or impaired psychomotor performance are at risk for developing alcohol use disorders [5].

Genetic susceptibility interacts with experience to determine outcome [6]. Exposure to childhood adversity is now considered as a major experiential risk factor. There is a dose-dependent relationship between the number of adverse childhood experiences, such as recurrent physical abuse or recurrent emotional abuse, and risk for alcoholism or drug abuse [7]. The understanding of this relationship is highly relevant.

Cerebellum is a key target of alcohol toxicity in the central nervous system [8]. Gait disturbances and ataxia in lower limbs are common both in acute intoxication and in chronic alcoholism. As a result of the closed loops between cerebellar circuitry and cerebral cortex, cerebellar damage might contribute to the visuospatial difficulties and impaired verbal learning observed in alcoholism [9].

Individual differences in cerebellar morphology seem to play a role in the development of alcohol dependence and substance abuse [10]. Cerebellar vermis is particularly vulnerable to alcohol abuse [11]. The anterior vermis is typically affected both in case of fetal exposure and in adults [12, 13]. Atrophy of this region of the cerebellum is one of the first consequences visible on brain magnetic resonance imaging. Other areas of the cerebellum such as the flocculonodular lobe and the central white matter also show volume loss [14]. A 42% atrophy of vermal white matter has been found in ataxic alcoholics and appears to significantly contribute to ataxia [14]. However, cerebellar degeneration may be discovered in alcoholics without signs of ataxia [15]. Purkinje cell loss and impaired dendritic networks in the molecular layer are common [16, 17]. Successive episodes of ethanol withdrawal also causes a loss of Purkinje cells [18]. Granule cells are less vulnerable than Purkinje neurons [19].

The mechanisms of ethanol-induced cerebellar degeneration include thiamine deficiency and defects in energy production, deficits in growth factors, and apoptosis [20]. Thiamine is a cofactor of key enzymes of the energy metabolism. Not only chronic alcoholics present a deficit in thiamine resulting from inadequate intake, but also ethanol inhibits the conversion into its active metabolite by blocking the pyrophosphokinase [21]. Thiamine deficiency contributes to the pathogenesis of Wernicke encephalopathy. Alcohol interacts with neurotrophins, whose roles in the developing and mature cerebellum are critical [22, 23]. Excitotoxicity is another detrimental actor of the cascade of events implicated in ethanol-induced cerebellar degeneration. Acute doses potentiate GABA-A receptors, hence, the antianxiety effect. Intranuclear administration of ethanol decreases the levels of GABA and raises the concentrations of nitric oxide [20]. Chronic

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exposure increases the sensitivity to NMDA, leading to a deleterious rise in calcium levels in neurons. The abrupt discontinuation of alcohol drinking decreases GABA transmission, a factor acting synergistically with the up-regulated NMDA activity to cause the symptoms of withdrawal syndrome [20]. Alcohol targets also glial cells, especially astrocytes, with consecutive deficient glial support to neurons.

In this issue, a careful examination of the morphology of the anterior cerebellar vermis by Anderson et al. [6] reveals that a high-level consumption of hard liquor in young adults who have not previously showed alcohol dependence is associated with a marked thickening of lobule I (lingula). Increased lingula thickness is found in case of greater consumption of drugs and hard liquor, particularly in physically maltreated subjects who have consumed more alcohol and have used drugs more frequently than controls.

Individuals with thicker lingulas may consume hard liquor preferentially, as they may be less susceptible to vestibulocerebellar effects. The authors report that exposure to emotional maltreatment (EM) does not increase rates of drug use, even though it is associated with greater symptom ratings of depression and anxiety as compared to exposure to physical maltreatment (PM). Strong interactive effects of exposure to early adversity and lingula thickness on drug and alcohol use are reported.

These findings are unexpected, since chronic use of alcohol or fetal exposure typically causes atrophy of this cerebellar region. A thick lingula results from the in utero fusion of lobule I and II. So far, cerebellum has not been viewed as a main brain region associated with risk for substance abuse. The authors propose that individual differences in morphology of the anterior cerebellar vermis may serve to increase risk for alcoholism and drug abuse in young adults. Indeed, individuals with thick phenotypes may have a blunted vestibulocerebellar response to alcohol, making a link between a vermal phenotype and exposure to early adversity. Several experimental findings reinforce the hypothesis of Anderson et al. of a link between morphology/dysmorphology of the lingula, EM/PM, and the degree of ongoing alcohol or drug use. For instance, the vermis, through its fastigial projections to substantia nigra and ventral tegmental area, modulates the turnover of dopamine in the caudate and nucleus accumbens [24]. Another link is the recently described effect of orexins (a family of hypothalamic neuropeptides involved in addiction) upon cerebellar nuclei [25]. These novel findings provide new insights into the understanding of experientially sensitive risk factors for enhanced alcohol and drug use. They expand the growing number of observations of interactions

between genetic and environmental etiologies in the spectrum of cerebellar disorders [26].

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