

The psychobiological regulation of social cooperation

Dynamic interactions between multiple factors underlie alcoholism, including recently described neuroregulatory influences (pages 654–657).

Because of the controversial nature of the results described by Tiihonen et al. in this issue of Nature Medicine, two alcoholism experts (C. Robert Cloninger and David Goldman) were asked to contribute different perspectives on the research.

Recent studies in Finland suggest that individuals with the most frequent type of alcoholism can be distinguished from other alcoholics and from healthy volunteers by a deficit in dopaminergic neurotransmission. The dopaminergic deficit, somewhat similar to that seen in Parkinson's disease, was observed in type 1 alcoholics, who have adult onset of alcoholism and no antisocial behaviour. The density of striatal dopamine transporter sites, which allow re-uptake of dopamine into presynaptic terminals, was markedly lower in type 1 alcoholics than in type 2 (antisocial) alcoholics or healthy controls (Tiihonen *et al.*, this issue of *Nature Medicine*)¹. Another study showed that type 1 alcoholics also had low striatal dopamine D2 postsynaptic receptor density and affinity. Dopamine transporter density was only slightly higher in antisocial (type 2) alcoholics than in controls, so the observed differences between alcoholics and others were not a consequence of heavy drinking.

The two subtypes of alcoholism studied in Finland were originally distinguished in studies of Swedish adoptees and families in the United States on the basis of their clinical features and patterns of inheritance². Type 1 alcoholism is characterized by rapid development in adulthood of dependence on the anxiety-reducing effects of alcohol, and is not associated with antisocial behaviour. In contrast, type 2 alcoholism is more strongly heritable and characterized by teenage onset of antisocial behaviour and recurrent abuse of many substances for their euphoriant effects.

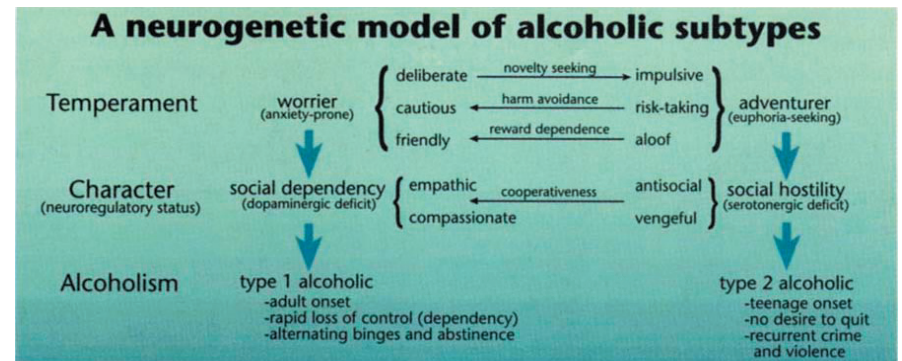
In addition, the two alcoholic subtypes can be distinguished by differences in heritable personality traits² (see figure). Early initiation of drinking, as in type 2, is most likely in individuals with impulsive-aggressive temperaments³. Such impulsive-aggressive people are high in novelty seeking (that is, impulsive, rule-

breaking, and quick-tempered) and low in harm avoidance (i.e., risk-taking, fearless, optimistic). In contrast, late initiation of drinking, as in type 1, is most likely in individuals who are anxiety-prone and socially conforming. Such socially anxious individuals are low in novelty seeking (that is, deliberate, rigid, and orderly) and high in harm avoidance (that is, worried, fearful, pessimistic).

The psychobiology of these personality traits has been studied in patients with Parkinson's disease. Patients with idiopathic Parkinson's disease have a lifelong pattern of being low in novelty seeking;

uptake in the left caudate ($r = 0.68$, $P < 0.03$). This is comparable to the findings in Finnish alcoholics, where striatal dopamine uptake is lowest in type 1 alcoholics, who are expected to be low in novelty seeking.

In contrast, serotonergic deficits have been consistently observed in type 2 alcoholics (see figure). Children at risk for type 2 alcoholism are usually high in novelty seeking, low in harm avoidance and also low in a separately inherited temperament factor called reward dependence (that is, they are aloof, cold and unappreciative). Reward dependence involves individual differences in sensitivity to social cues, that is, giving and receiving signs of appreciation³. It is positively correlated ($r = 0.64$) with the ability of serotonin to stimulate



they have been described as deliberate, stoic, reliable and inflexible both premorbidly and after the onset of motor symptoms⁴. Parkinsonian patients do not differ in harm avoidance or other aspects of personality from others with comparable motor disability. The low novelty seeking of Parkinsonian patients results in reduced appetitive approach behaviour throughout their life. For example, patients with Parkinson's disease are only half as likely to have ever smoked as other people, and their risk and extent of smoking has a weak but consistent correlation ($r = 0.3$, $P < 0.01$) with their novelty seeking scores⁵. In addition, the correlation between personality traits and striatal uptake of 18-fluoro-dopa was measured by positron emission tomography in nine patients with idiopathic Parkinson's disease⁶. Dopa uptake in the caudate was positively correlated with novelty seeking, but not the other temperament traits. Novelty seeking was most strongly correlated with

the ritanserin-sensitive (5-HT₂) formation of inositol monophosphate in platelets⁷. When followed prospectively, individuals who have impulsive-aggressive and socially insensitive temperaments are often, but not always, uncooperative and disruptive as children and become hostile poly-drug abusers as adolescents³. As young adults, they are likely to commit violent crimes³ and to receive psychiatric diagnoses of antisocial personality disorder⁸ and type 2 alcoholism⁹. In other words, they have a character trait of uncooperativeness involving lack of empathy, social tolerance, compassion and moral principles¹⁰. This uncooperativeness is associated with hostility and depression, frequently leading to serious aggression and/or suicide attempts¹¹. The deficit in character and social skills has been consistently associated with deficits in serotonergic neuroregulation, including decreased availability of the serotonin precursor tryptophan, reduced serotonin concentra-

tions in platelets and low cerebrospinal fluid levels of 5-hydroxyindoleacetic acid, which is highly correlated with serotonin metabolite levels in frontal neocortex¹¹⁻¹³.

Temperament traits are moderately stable throughout life, whereas character develops in a stagelike manner from infancy through adulthood¹⁴. Transitions between levels of maturity in character and social skills are nonlinear functions of temperament, social learning, specific genetic factors and random life events^{10,14}. In particular, low reward dependence and impulsive-aggressive traits increase the risk of uncooperative character, but the correlation of uncooperativeness with any one of its temperamental antecedents is not strong⁸. In children and adults, low cooperativeness is correlated moderately with low reward dependence ($r = 0.54$) and weakly with each of three separately inherited components of impulsivity — low harm avoidance ($r = 0.28$), low persistence ($r = 0.18$) and high novelty seeking ($r = 0.10$)^{3,14}. Like character, but not temperament, the serotonergic deficit is also moderately influenced by family environment¹⁵. Although the serotonergic deficit is

consistently correlated with antisocial character traits, it is only indirectly and inconsistently correlated with temperament traits, such as high novelty seeking¹⁶, low harm avoidance¹⁶, other measures of impulsivity¹³, or history of aggressiveness¹¹.

Although the temperament dimensions described here are inherited independently¹⁷, they have environmental influences in common. The response to the same environmental stimulus, such as social contact with a stranger or having a drink of alcohol, is regulated by multiple personality dimensions^{3,14}. Consequently, the different components of personality become correlated and the emerging network of relations organizes personality into relatively stable configurations. These stable configurations, such as alcoholic subtypes, are called attractors in complex adaptive systems¹⁴. As an example at the psychological level, personality configurations in which low novelty seeking is combined with high harm avoidance are much more stable than configurations in which both are high because the latter produces approach-avoidance conflicts about social conformity². When combined, low nov-

elty seeking and high harm avoidance facilitate stability in socially conforming behaviour and allow extended time for maturation of social competence and cooperativeness before onset of drinking¹⁴.

At a neurobiological level, another consistent finding is that the levels in the cerebrospinal fluid of monoamine metabolites are all positively correlated with one another^{18,19}. Accordingly, when central serotonergic turnover is low, as in type 2 alcoholics, dopaminergic turnover is also likely to be low, but not invariantly²⁰. However, the positive correlations between the serotonin metabolite 5-hydroxyindoleacetic acid and the dopamine metabolite homovanillic acid in nearly all brain regions do imply that serotonergic stimulation facilitates dopamine release, at least when basal activity levels are low, as in type 2 alcoholics¹⁹. This facilitatory interaction between serotonin and dopamine release can be demonstrated by stimulating serotonin receptors selectively. For example, m-chlorophenylpiperazine (mCPP), a partial agonist at serotonin receptors, particularly 5-HT_{2c} sites, produces euphoria and a desire to resume drinking in many abstinent type

Dopamine transporter, alcoholism and other diseases

The discovery of dopamine transporter density difference in alcoholics has implications for mechanisms of vulnerability and relapse (pages 654-657).

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From a public health perspective, common, aetiologically complex diseases such as alcoholism are among the most important traits for identifying biological markers or genetic variants (alleles) influencing vulnerability. The elucidation of the mechanisms of psychiatric diseases may also lead to an improved understanding of how the brain works.

As shown by Tiihonen *et al.* in this issue of *Nature Medicine*, the technique of *in vivo* SPECT is a window into the brain with the rare capability of displaying region-specific differences in brain metabolism and neurotransmitter function. The reductions of striatal dopamine transporter density in the ten non-violent alcoholics studied by Tiihonen *et al.* are probably indicative of a state of alteration, rather than an inherited trait difference in these alcoholics. If we presume that alcoholism is aetiologically heterogeneous, it is highly unlikely that the lower dopamine transporter densities which were consistently observed could reflect a genetic trait difference. Furthermore, striatal dopamine transporter densities were not altered in a group of

nineteen impulsive violent alcoholics who probably would be classified as Cloninger type 2, early-onset alcoholics. It is these type 2 alcoholics who show evidence of the strongest genetic loading².

The Tiihonen *et al.* dopamine transporter density results, obtained in relatively small numbers of alcoholics who were abstinent for a minimum of two months, obviously require confirmation. If confirmed, they would indicate that alcohol exposure or other experience common to alcoholics is capable of inducing a long-lasting alteration of function in brain dopamine pathways. This effect of experience could underlie alcoholics' long-lasting vulnerability to relapse and the rapid reinstatement of high levels of alcohol consumption in alcoholics who do relapse.

Because of the involvement of dopamine pathways in drug-mediated reinforcement and the substantial heritability of alcoholism, it is logical, and probably inevitable, that naturally occurring variants

of genes involved in dopamine function will be found that mediate differential vulnerability in some alcoholics. Clearly, variants of individual genes can produce complex behavioural phenotypes. Examples would include hypoxanthine-guanine phosphoribosyl transferase in self-mutilatory behaviour, the monoamine oxidase A stop codon variant in X-linked behavioural disorder³, thyroid hormone receptor variants in attention deficit-hyperactivity disorder (ADHD)⁴ and the inactive aldehyde dehydrogenase 2 allele (*ALDH2*²) in alcoholism vulnerability. *ALDH2*² is abundant in East Asian populations and profoundly influences vulnerability to alcoholism, even in Koreans and Chinese who have immigrated to North America⁵.

The Tiihonen *et al.* study did not include genetic marker or direct gene scanning results for the dopamine transporter gene or other genes involved in dopamine function. This includes the DRD2 dopamine receptor, which they speculate may be involved in the difference in transporter expression they observed.

The association of the DRD2 'A1' allele to

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2 alcoholics, but only anxiety in normals and other alcoholics^{12,21}. In contrast, noradrenergic agonists like yohimbine produce anxiety but no craving for alcohol²¹.

The recent Finnish findings of a dopaminergic deficit in type 1 alcoholics are similar to earlier findings about temperament and substance use in Parkinson's disease. The Finnish findings are the first identification of a specific neuroregulatory deficit in type 1 alcoholics. In contrast, type 2 alcoholics have extensive prior evidence of a serotonergic regulatory deficit, so the finding that striatal uptake of dopamine is only slightly greater in type 2 alcoholics than normals supports and extends other work in Finland and elsewhere^{11,20}. Together the psychobiological findings of individual differences in type 1 and type 2 alcoholic subtypes, Parkinson's disease and related personality configurations make clear that alcoholism results from nonlinear dynamic interactions among multiple neuroregulatory and environmental factors, no one of which is necessary or sufficient to cause disorder.

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alcoholism is controversial. It is difficult to imagine how the linkage of the non-functional 'A1' marker to a functionally divergent *DRD2* allele in a minority of alcoholics could lead to a reduction of dopamine transporter density in most alcoholics. Several intensive direct gene analysis studies of *DRD2* have yielded three relatively rare amino acid substitutions⁶ but no receptor variants that could account for a *DRD2* marker association to a large fraction of alcoholics, for example, results reported by K. Blum, E. Noble and colleagues in 1990 that two-thirds of alcoholics have the A1 allele. The *DRD2* genotypes of the subjects studied by Tiihonen *et al.* would be of some interest; a *DRD2* association study which was conducted in Finland found no association of the 'A1' allele to alcoholism⁷ but that study did not incorporate brain-imaging results.

Given that a difference was observed in dopamine transporter density and that the *DRD2* gene has been studied fairly intensively, the next logical place to look for a genetic difference may be the dopamine transporter (*DAT1*) gene. Genetic studies on the dopamine transporter have been reported across a range of syndromes in which dopamine dysfunction has been suggested and these studies take advantage of a highly informative variable number of tandem repeats (VNTR) marker at the

DAT1 locus⁸. Several of these *DAT1* linkage studies have been positive. Although *DAT1* does not show linkage to schizophrenia⁹ or polysubstance abuse⁸, the nine copy *DAT1* VNTR repeat was approximately twice as abundant in individuals with cocaine-induced paranoia as compared with other cocaine abusers¹⁰ or parents of children with ADHD¹¹. Using the haplotype relative risk strategy¹² in parent-child trios, Cook *et al.* observed that the ten-repeat allele was associated with ADHD¹¹. Kelsoe and colleagues have reported results indicating linkage between *DAT1* and bipolar affective illness with lod scores of 1.3 in the Amish (World Congress on Psychiatric Genetics in 1993) and approximately 2.4 in another family (Park City Molecular Psychiatry meeting in 1995; J. Kelsoe, personal communication). Taken together, these *DAT1* linkage and association results emphasize the importance of direct screening of patients for variation in dopamine transporter density, as accomplished by Tiihonen *et al.*, as well as functional studies of the dopamine transporter and direct scanning of the *DAT1* gene for inherited variants that may influence vulnerability to alcoholism and other psychiatric diseases.

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