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Substance-specific symptoms and general liability to addiction

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And a little bit of this'd get you up

And a little bit of that'd get you down

Mark Knopfler "Junkie Doll" (*Sailing to Philadelphia*)

Abuse of different psychoactive substances frequently co-occurs – if not as diagnosable disorders then at the symptom level. The abuse and dependence symptoms for different substances may develop sequentially, along with changes in the person's drug use repertoire, and/or coexist, reflecting concurrent use. Comorbidity for any two disorders has been mathematically interpreted in several association models grounded in the concept of multifactorial *liability*, a latent (unobserved) trait resulting from all factors influencing the probability of the disorder (1,2). The models differ in the relationships' causality direction and in thresholds of liability at which one disorder (or liability) may influence risk for another. The relationships forming these models can be drawn to several not necessarily mutually exclusive sources: (a) both disorders being alternate manifestations of, or located on, the same liability continuum; (b) a third disorder, or another source(s) of shared liability, increasing risk for or causing both; and (c) one disorder increasing the risk for or causing another, including reciprocal effects. In particular, tests of these models to account for comorbidity between alcohol and drug dependences suggested common liability as the best explanation (3).

This is not inconsistent with genetic data. Twin research suggests that whereas liabilities to addictions form two distinct groups that correspond to licit and illicit substances, each with a single additive genetic component of variance (that represents variation in many genes) accounting for most of covariation between symptoms of abuse/dependence across respective substances, these two genetic factors are highly correlated (4). The distinctiveness of these factors is obviously not related to anything specific to the substances per se, different as they are within the groups. Rather, it is a reflection of social norms dividing use of psychoactive substances into two categories: one legal, and the other that involves norm violation that amounts to breaking the law. It is noteworthy that this clearly *environmental* factor induces different patterns of *genetic* relationships between and within the two substance groups. From the standpoint of this common, or general (non-drug-specific) liability to addiction (GLA) model, the pattern of drug use initiation – frequently from licit to illicit, or from "softer" to "harder" substances, but in many cases reverse – is variable and opportunistic, rather than uniform and developmentally deterministic (5) as posited by the "gateway hypothesis" (GH) (6). Despite that, and even though the GH addresses only sequential drug use initiation and does not extend to addiction disorders, while initiation does not account for addiction risk, the GH has been the foundation of many drug-related policy and research decisions. Obviously, the GH, focused on drugs per se, particularly on the inconsistently defined "gateway drug" (alcohol, tobacco and marijuana have all been proposed as such), calls for controlling supply of that substance and substance use behavior. In contrast, the GLA theory focuses on social behavior and behavior regulation precursors

and concomitants of drug abuse, which is one possible developmental manifestation of socialization failure.

A study by Vrieze et al. (7) in this issue of the Journal contributes new information pertaining to comorbidity of addictions by exploring developmental changes – from 14 to 29 years of age – in the relationships among the symptoms of abuse of and dependence on alcohol, tobacco and marijuana. The study is conducted in a population-based twin sample, enabling tests of biometric (behavior genetic) models. The results show that the relationships among symptoms across substances decrease over years, as does the genetic commonality among them. This is consistent with the GLA theory, inasmuch as earlier experimentation, use and symptomatology are reflective of general norm violation associated with any substance use before legal drinking/smoking age, whereas at a later age alcohol and tobacco become legal while marijuana remains illegal. Indeed, it seems that the contribution of the common factor in the symptom variance drops by adulthood (age 20 in this study) but remains relatively stable thereafter.

The authors note that the decrease in associations among symptoms for different substances contradicts the GH because “the initial drug use would cause them to use other drugs” over time. A counter-argument may be that it is difficult to interpret these data unequivocally as supporting or contradicting the GH, because the study does not analyze information on “hard” drugs. It is transition to the latter from marijuana, the “gateway” drug in the current applications of the GH, that is considered the critical “stage” in the “gateway” progression. According to the original formulation of the GH (6), however, the first “stage” is alcohol/tobacco use, which is followed by transition to marijuana. Thus, if the GH is true, as use of these substances grows over time, the correlations with marijuana use should grow, as more alcohol users will transition to marijuana. This pattern is different from those observed in the study, contrary to the GH. It should be emphasized, however, that the study operated with symptoms of the disorder rather than with substance use initiation, the topic matter of the GH. Although likely correlated, the sequences of substance use initiation and development of disorder symptoms are not necessarily aligned exactly. It is the latter, however, that are of medical importance. Accordingly, it is the fact that the data are consistent with the general liability theory, this time with its developmental aspect, that is an important conclusion of the paper. This conclusion is consistent with other reports indicating incongruity of the GH with empirical data (5).

Correlations across substances are similar to those in the recent study by Palmer et al. (8), with participants younger than the last assessment age in the Vrieze et al. study, but somewhat lower than those estimated in prior research by Kendler et al. (2007) for a sample that is older on average and, if the age trend reported by Vrieze et al. is maintained, should have even lower correlations. The highest correlations in the Kendler et al. study were observed between symptoms across illicit substances, cannabis and cocaine, of which only the former was examined in the Vrieze et al. and Palmer et al. reports. It is possible that longitudinal trends for commonalities among liabilities to abuse of licit and illicit drugs are different. That, however, cannot explain the discrepancy between the observations of a decline in heritability for nicotine in the present study and its growth in a previous report from the same group (9). Similarly, heritability growth with age has also been observed for externalizing behaviors (10) strongly associated with the GLA. Further research seems necessary to resolve these discrepancies.

It should also be taken into account that comorbidity may not be optimally addressed when using symptoms of the disorder that do not reach the diagnostic threshold. On the other hand, although the studies discussed operated with symptoms rather than diagnoses, substantial proportions of the samples qualified for a diagnosis, whereas dichotomizing the

phenotypes by using diagnoses would reduce analytic power. The dimensional symptom count is also more consistent than the categorical diagnosis with the concept of continuous liability. Development of quantitative indices that would cover the entire range of liability phenotypes in the population, including non-symptomatic ones (11), would be a logical extension of the findings identifying general liability to addiction. Drug-specific risks notwithstanding, addressing GLA in both research and intervention could be an efficient approach to the addiction problem.

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References

1. Neale MC, Kendler KS. Models of comorbidity for multifactorial disorders. *Am J Hum Genet.* 1995; 57:935–953. [PubMed: 7573055]
2. Falconer DS. The inheritance of liability to certain diseases, estimated from the incidence among relatives. *Annals Hum Genet.* 1965; 29:51–76.
3. Rhee SH, Hewitt JK, Young SE, Corley RP, Crowley TJ, Neale MC, Stallings MC. Comorbidity between alcohol dependence and illicit drug dependence in adolescents with antisocial behavior and matched controls. *Drug Alcohol Depend.* 2006; 84:85–92. [PubMed: 16413148]
4. Kendler KS, Myers J, Prescott CA. Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. *Arch Gen Psychiatry.* 2007; 64:1313–1320. [PubMed: 17984400]
5. Vanyukov MM, Tarter RE, Kirillova GP, Kirisci L, Reynolds MD, Kreek MJ, Conway KP, Maher BS, Iacono WG, Bierut L, Neale MC, Clark DB, Ridenour TA. Common liability to addiction and “gateway hypothesis”: Theoretical, empirical and evolutionary perspective. *Drug Alcohol Depend.* 2012; 123:S3–S17. [PubMed: 22261179]
6. Kandel D. Stages in adolescent involvement in drug use. *Science.* 1975; 190:912–914. [PubMed: 1188374]
7. Vrieze SI, Hicks BM, Iacono WG, McGue M. Genetic influence on the co-occurrence of alcohol, marijuana, and nicotine dependence symptoms declines from age 14 to 29. *Am J Psychiatry.* 2012; XXX:XXX–XXX.
8. Palmer RH, Button TM, Rhee SH, Corley RP, Young SE, Stallings MC, Hopfer CJ, Hewitt JK. Genetic etiology of the common liability to drug dependence: Evidence of common and specific mechanisms for DSM-IV dependence symptoms. *Drug Alcohol Depend.* 2012; 123:S24–S32. [PubMed: 22243758]
9. Tully EC, Iacono WG, McGue M. Changes in genetic and environmental influences on the development of nicotine dependence and major depressive disorder from middle adolescence to early adulthood. *Devel Psychopathol.* 2010; 22:831–848. [PubMed: 20883585]
10. Bergen SE, Gardner CO, Kendler KS. Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. *Twin Research Hum Genet.* 2007; 10:423–433. [PubMed: 17564500]
11. Conway KP, Levy J, Vanyukov M, Chandler R, Rutter J, Swan GE, Neale M. Measuring addiction propensity and severity: the need for a new instrument. *Drug Alcohol Depend.* 2010; 111:4–12. [PubMed: 20462706]