Risk and resistance perspectives in translation-oriented etiology research

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Abstract

Risk for a disorder and the mechanisms that determine its elevation, risk factors, are the focus of medical research. Targeting risk factors should serve the goal of prevention and treatment intervention. Risk, however, is but one of the aspects of liability to a disorder, a latent trait that encompasses effects of all factors leading to or from the diagnostic threshold. The coequal but opposite aspect of liability is resistance to a disorder. The factors that increase resistance and thus enable prevention or recovery may differ from those that elevate risk. Accordingly, there are nontrivial differences between research perspectives that focus on risk and on resistance. This article shows how this distinction translates into goals and methods of research and practice, from the choice of potential mechanisms tested to the results sought in intervention. The resistance concept also differs from those of “resilience” and “protective factors,” subsuming but not limited to them. The implications of the concept are discussed using substance use disorder as an example and substantiate the need for biomedical research and its translation to shift to the resistance perspective.

Keywords

Resilience, Protective factors, Research paradigm, Phenotype measurement, Malleability

The World Health Organization (WHO) defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [1]. Health research, however, is naturally driven by the capabilities and interests of its main consumer, the medical profession, and by the needs of its beneficiaries, the patients. Those interests and needs, as well as allocation of limited resources, have historically been mainly in managing the disease rather than maintaining health. With rare exceptions, even prevention has not been the major goal of medical research.¹

Accordingly, health research is categorized mainly by disease, based on diagnostic systems that are

Implications

Practice: The approach described in this paper can be used to strengthen or ensure the studies’ ability to discover factors leading to prevention of and recovery from a disorder.

Policy: Funders who wish to improve the likelihood of detecting factors causing recovery and preclude pathogenesis of a disorder may recommend adoption of the approach described in the paper.

Research: Specifically targeting mechanisms that increase resistance to a disorder, as opposed to risk factors, enabled by the approach described herein, may improve the likelihood of obtaining practically significant research results.

needed for clinical work and the economic aspect of healthcare (e.g., practitioners generally cannot be compensated for the absence of disease) but frequently inadequate in research. It has been recognized, for instance, that psychiatric disorders are not unique discrete entities, and even psychotic disorders may represent continua (with hallucinations and delusions not uncommon in “normal” individuals) [2]. This has been recently addressed by the National Institute of Mental Health in setting the goal to “[d]evelop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures” [3]. Furthermore, it was stated that “NIMH will be re-orienting its research away from DSM categories” [4]. Nevertheless, this reorientation pertains more to the “crisis of psychiatric classification” [5], which currently satisfies neither clinicians nor researchers, than to the disease outlook of biomedical science and medical practice in general. The categorically defined disease perspective prevails.

Health research is thus typically focused on the etiology of *disease* rather than on etiology of health. The disease focus and the difficulties in identifying the *health phenotype* as other than the *absence of disease* are at least two reasons why the WHO goal of maintaining and perfecting health is not vigorously pursued.

¹ vaccination against some infections is a discussion point further in the paper

The practical goal is the elimination of disease causes, rather than employing causes of health and prevention. Indicating a further distancing of research foci from health, it has been observed that “[o]vervaluing translational research is detracting from an equivalent appreciation of fundamental research of broad applicability, without obvious connections to medicine” [6].

This dissociation of medical research from its application goal may in part be due to its current low rate of successful translation. In the not-so-distant past of relatively rapid progress, when attention was focused on infections and “genetic” (monogenic or Mendelian) disorders, the cause of a disorder denoted the cause of *variation in risk* for a disorder. Risks for these diseases covary almost exactly with a single environmental or genetic variable, the presence/absence of an agent, be it an environmental pathogen or an allele. Those “simple” diseases could be considered a low-hanging fruit from the etiology research viewpoint, yet many of them are still far from being conquered. Even when a single potent factor can be identified, as in monogenic disorders, translation is often infeasible. Nonetheless, studies in the complex (multifactorial) disorders have followed the same scheme despite the absence of correspondence between any single factor and the phenotype.

This paper considers possible solutions to these issues, juxtaposing two general research approaches: the commonly used *risk/disease* perspective, and, symmetric but distinct, the *resistance/health* perspective. Drug addiction (substance use disorder; SUD) is used as the main illustrative example because of its multifaceted complexity and parallels with other health problems as well as normal behavior. Addiction is a recognized complex psychiatric disorder, but a necessary prodromal condition for its development, drug use, is often voluntary and deliberate. Drug addiction also has similarities with infectious diseases: drugs are known environmental pathogens that are necessary for its development and virtually ubiquitous. Exposure to drugs, however, is less random: it is frequently sought rather than passive, a behavioral manifestation rather than a purely environmental factor. The majority of diagnostic SUD symptoms are drug-related *behaviors*, which may or may not reflect neurobiological changes, and the main phenotypic manifestation of addiction is behavioral, persistent drug-seeking despite negative consequences.

This article introduces a phenotypic conceptualization that is conducive to the detection of factors related to a disease-free state and recovery from a disorder, and discusses possible approaches to its implementation. As such, its topic pertains to Type 0 translation research (Table 1), focused on producing translatable results.

LIABILITY: RISK AND RESISTANCE PERSPECTIVES

As with other complex diseases, various sources of phenotypic heterogeneity in addiction complicate the search for targets for prevention and treatment. Even

for a single drug, there are hundreds of distinct combinations of symptoms corresponding to the same drug-specific SUD diagnosis [7]. Different factors may influence the pathogenetic process at its different stages: drug use initiation, habitual consumption, and the clinical disorder and its outcome. There is no natural gap between the norm and pathology. Physical dependence, which is an organismic response to drug exposure (e.g., sometimes resulting from pain treatment), does not necessarily entail drug abuse and addiction as behavior [8]. The lack of a consistent definition of the phenotype is a barrier in addiction research and intervention.

To deal with this complexity, individual risk for addiction and the disorder itself can be viewed as individual values (phenotypes) of a continuous variable (trait) termed *liability* [9]. This latent (unobserved directly) trait encompasses the effects of all factors influencing the probability and severity of a disorder. If measured, it “would give us a graded scale of the degree of affectedness or of normality” [9]. Liabilities to complex (multifactorial) disorders including addiction vary in the population due to individual differences in multiple genes as well as environmental factors. It is in that sense that disorders are termed multifactorial. Each factor contributes a small proportion to liability variance, likely resulting in a normal distribution, according to the central limit theorem, akin to IQ (an index of a latent multifactorial trait), or stature and body mass (observed multifactorial traits) (Fig. 1). The liability phenotypes of individuals diagnosed with a disorder (affected) are generally beyond a certain point on the liability scale, termed the threshold. The liability-threshold model is a prevailing conceptualization for the multifactorial diseases in human genetics [10–12]. It covers the entire range of phenotypes where the maximum value (“1”) could be assigned either to the onset of the disorder or, if the suprathreshold range of liability is included, to its highest severity. However, there are no face-valid observable *a priori* indicators that would allow assessing the individual liability value of “0” (a lifetime outcome of “no disorder” is not sufficient). The SUD liability phenotype is also age-dependent, and its development (and SUD pathogenesis) is superimposed on the physiological and behavioral ontogenesis [13].

Liability-influencing factors that are statistically associated with elevated risk—e.g., an allele or an adverse environmental condition associated with a disease phenotype—are commonly viewed as risk factors [14]. Similarly, the factors *decreasing* the probability of disorder can be designated *resistance* factors, risk and resistance being the two sides of the liability coin.²

Resistance factors extend beyond those that help rebound from a stressor to the prestress state, i.e., those corresponding to *resilience*, which is commonly defined

² It should be noted that “resistance” herein denotes a construct that is entirely different from the same name construct in the recent article by Kendler and Myers [15], which is based on scaling “lifetime maximal use of the relevant substance.”

Table 1 | Translational research stages

Type	Type 0 translation (T0)	Type 1 translation (T1)	Type 2 translation (T2)
Definition	Research resulting in discoveries that could be applied (translated) in prevention or treatment intervention	Moving from bench to bedside. Applying biomedical and social findings to development of methods and programs of intervention.	Implementation of methods and programs of intervention.
Type	Type 3 (translation) (T3)	Type 4 translation (T4)	Type 5 translation (T5)
Definition	Determining whether efficacy and effectiveness trial outcomes can be replicated under real-world settings.	Wide-scale implementation, adoption and institutionalization of new guidelines, practices and policies.	Translation to global communities. Involves fundamental, universal change in attitudes, policies and social systems.

as “the process of, capacity for, or outcome of successful adaptation despite challenging or threatening circumstances” [16]. That definition refers to the facet of *resistance* that is contingent on identifiable adverse influences external to the organism and is limited to successful adaptation to such factors. Thus, if resilience were always defined in relation to a *particular disorder* (as opposed to nonspecific ability to withstand adversity), it would be subsumed by resistance, a more general concept. However, in contrast to resistance as a facet of liability to a particular disorder, resilience is often not so delimited but understood as nonspecific “successful” adaptation to life tasks in the face of social disadvantage or highly adverse conditions” ([17], p. 163) in general, a largely descriptive and hard-to-operationalize concept. It is *inferred* upon observation of such adaptation, rather than being amenable to measurement at any point. In the original physics sense of the term resilience (and its analog in psychopathology), it is the ability of the material to return to its prior state upon removal of a stressor (or, in psychopathology, to withstand adversity—cf. risk factor), which corresponds to the *neutral* position or indeed the absence of stress. Phenotypic *resistance* cannot be viewed as merely (the degree of) returning to, or keeping, a prestress condition. It also includes the effect of factors that may preclude the very exposure to a

stressor, allow a nonpathological adaptation to it, and preclude relapse upon cessation of the pathological condition (e.g., addictive behavior). Defined as a latent variable, resistance is also measurable.

Whereas resilience pertains to the reaction to external adversity, the concept of resistance also covers factors that offset a high *organismic* “adversity.” Moreover, of particular interest are the environmental factors capable of offsetting high genetic (organismic) predisposition to the disorder. Thus, while it is recognized that adversity is an important facet of the environment and the organismic response to it, resistance factors also include those that *increase organismic resistance* to the disorder, including those whose action *precedes, prevents, and/or* limits exposure to a pathogen (e.g., drugs), as well as enables absence of relapse upon recovery.

The concept of resilience is also not readily applicable to addiction. Involvement with drugs that leads to addiction is driven by seeking their reinforcing effects—sometimes exactly for coping with stress, as self-medication [18], so that drug abuse outcome is sometimes viewed as a (mal)adaptive response to that nonspecific stress, and the absence thereof is considered manifest resilience [19]. In other words, it is unclear whether the adversity is the condition that calls for self-medication or if it is exposure to drugs (which,

Fig. 1 | Liability: Detectability of risk and resistance factors. The “1” in parentheses under the threshold value refers to the situation where the target phenotype is the disorder in general, with the severity distribution drawn to and collapsed at that point

in turn, could be merely the presence of drugs in the environment, or drug consumption).

Importantly, while risk and resistance are the symmetric coequal liability aspects, growing inversely along the liability scale, the discrete factors that are aggregated at the ends of the liability distribution may be entirely different. *Resistance factors are not necessarily the same as the risk factors* (but with the opposite sign, or the absence thereof, or alternative variants), which differentiates between resistance and *protective* factors. “Protective” factors, commonly conceptualized as “opposite ends of the same continuum [as risk factors]” (hence effectively defined by the latter) or, alternatively, those that “moderate or buffer the effects of risk factors” (hence referenced to the latter’s action) ([20], p. 57), are another subset of resistance factors. The sets of factors conveying elevated risk or enhanced resistance are likely to partially overlap (shown in Fig. 1 as D and D[−] in the sets—either discrete or, if a continuous variable, corresponding to the opposite ends of the distribution, one of the above varieties of protective factors). An example could be an allele in a diallelic polymorphism conveying enhanced resistance and the alternative allele that may convey elevated risk. The resistance and risk factor sets, however, may also have considerable differences. For instance, the alternative allele may be neutral, i.e., of no discernible phenotypic effect on the background of all other factors, rather than protective. Similarly, different ranges of values of a continuous variable can have a nonlinear, e.g., U-shaped, effect on a behavioral variable such as addiction resistance. The vertex of such a relationship may be at the minimum (from high to neutral or low to high again, as observed, e.g., for the relationship between oxytocin and trustworthiness [21]), or at the maximum (e.g., between age and susceptibility to peer influence [22]). A moderating variable (the other variety of factors defined as protective) can be considered a resistance factor only inasmuch as liability is decreased at one of its values (if discrete) or within its certain range (if continuous). In general, however, effects of moderators by definition are not independent but manifest in changes in the effects of other variables (which are viewed usually from the risk perspective—as offsetting a risk factor’s effect).

The genetics field has provided a stark example of the asymmetry of the disease-oriented approach. The once-popular transmission-disequilibrium test (TDT) [23], conducted in family-based genetic association studies, assesses genetic linkage and association by comparing alleles that are transmitted and nontransmitted from heterozygous parents to *affected* offspring, in order to detect those disproportionately *transmitted*. The “undertransmitted” alleles are disregarded, and *the unaffected offspring is not studied*. A symmetric or resistance-oriented approach could evaluate overtransmission of alleles to highly *resistant* offspring (or even unaffected offspring in the families where there

are both). That would seem to be more consistent with the health maintenance goal.

The low liability population may be very heterogeneous from the resistance standpoint, including those with high individual biologically based resistance, and those with no environmental exposure to the pathogen or whose biologically high risk has been offset by particular counteracting environmental factors (the dietary prevention of phenylketonuria, PKU, can serve as an example for the latter two situations). It is of high practical significance to distinguish between these possibilities and their mechanisms, which differ in their malleability and potential to provide usable information. This would facilitate search for prevention, treatment, and health maintenance approaches based on a set of factors having resistance-positive value rather than merely not adding to risk over its population average or removing a discrete risk factor like drugs (for addiction) or phenylalanine (for PKU).

Resistance (or risk, or resilience) is redundant when juxtaposed with the inclusive concept of liability [24]. It has, however, a heuristic value when contrasted with risk. The distinction would be trivial if the entirety of the liability distribution or, in Falconer’s words, both the “degree of affectedness” and that “of normality” were equally accessible and treated the same. They are not, however: the commonly used indicators of liability are disorder symptoms, whereas normality is largely collapsed into a single category of “no disorder” (virtually synonymous with “no symptoms,” because the symptoms below the number deemed necessary for the positive diagnosis are disregarded). It is difficult to conceptualize the gradations of the norm and conceive of its indicators that would allow its quantification—even in a limited way afforded by the symptoms for the gradations of affectedness (severity).

PRACTICAL IMPLICATIONS OF THE RESISTANCE PERSPECTIVE

The distinction between the risk and resistance perspectives is important particularly because it entails differences in approaches to the identification of respective factors—As illustrated in Fig. 1, aggregation and hence the probability of detection of risk and resistance factors differ in different portions of the liability distribution. Research that is focused on risk factors is likely to detect those with the strongest *risk*-increasing effects, averaged across the affected (or otherwise high-risk) individuals representing the *high end* of the liability distribution (5–10 % of the population). In contrast, phenotypes from the *low end* of that distribution, carrying the strongest *resistance*-increasing effects, are diluted by the heterogeneity of the typical control, sampled from 90 to 95 % of the population. While the goal is risk *reduction*, and maintaining and improving health, it is approached backwards: Factors commonly sought in research are those that *increase* risk and result in disease. Focusing on risk defines the search for discrete factors that *add* to the risk rather than *deduct* from it, with lower risk’s being mainly a fortuitous effect of

discrete risk factors' absence. For instance, in the above cited example of the TDT, this is the absence of the "risk" allele, regardless of the actual effect of an alternative allele present. Such alternatives—the "non-risk" factors (e.g., the alternative allele of a diallelic polymorphism), which are characteristic of the normal population—are likely to be of an average/neutral rather than a high resistance effect. Under the commonly used designs, detection of resistance factors is thus even more severely underpowered than the notoriously difficult risk/disease-oriented search. It is the resistance-raising factors, however, that may have the greatest translation potential, prevention value, and health impact.

Search for the resistance-increasing factors cannot be effected by merely reversing the polarity of risk-increasing factors, whether organismic (e.g., genetic) or environmental, as would correspond to the notion of protective factors. Indeed, the difference between the results of the risk and resistance approaches could be dramatic, as underscored by the rare studies that have applied the resistance perspective. For instance, heritability of the risk for alcohol use disorder is well-known to be substantial in both males and females [25, 26]. In contrast, when remission was the target phenotype, the phenotypic variance was composed of primarily (in females) or only (males) environmental contribution, mostly unique (uncorrelated between members of twin pairs) [27]. Only a small proportion of variance was shared in common between risk for the disorder and ability to remission. Therefore, despite the theoretical colocalization of risk and resistance on the same liability dimension, the difference between the risk and resistance perspectives may be as significant as dealing with different if correlated dimensions—likely because of the asymmetry of the end phenotypes as defined in practice (e.g., remission is not symmetric to the disorder diagnosis on the liability scale).

The need for changing the perspective may be gaining recognition. A recent article describes a perspective very similar to that discussed herein, "an emphasis on understanding how individuals remain healthy—'resilient' to disease... to decipher which of the hundreds of candidate second site mutations or environmental factors may be responsible for the buffering against disease" [28]. However, the Resilience Project implementing these ideas, while dealing with specific diseases (and thus with the realm of resistance rather than resilience), is focused on monogenic disorders that manifest in childhood, with plans to expand to other disorders, such as diabetes, cancer, and Alzheimer's disease—apparently contingent upon finding "clusters of genes that drive a disease." Nevertheless, while the liability phenotype in monogenic disorders, which is (almost) discrete, is easier to assess than addiction liability, the actionable resistance factors for monogenic conditions might be more difficult to find. The likely reason for that—despite the knowledge of the genetic etiology—is exactly that those factors would have to offset a strong effect of a

deleterious mutation, or influence its penetrance. The same single-mechanism-based approach, however, is even more difficult to implement with liability to a complex disorder such as addiction, in which there are no genes "that drive the disease." By the same token, finding environmental factors that offset high liability or determine high resistance to addiction appears more feasible. If the resistance perspective is being employed even for monogenic diseases, it certainly is timely for complex disorders, including SUD.

RESISTANCE TO DRUG ADDICTION

The sets of factors influencing drug use initiation, the development of physical dependence, and the development of addiction do not completely overlap. The former may include drug availability, peer behavior and pressure, psychological state, and home and social environment. Drug use has often been part of culture, which may be in a reverse relationship with the individual barriers against drug involvement. For instance, drug use by a role model (e.g., high-profile public figure) may attach legitimacy or permissibility to this behavior. The factors involved in the physiological response to drugs, on the other hand, are less influenced by social environment, as they include drug metabolism and neurochemistry of drug response. Many of behavior regulation mechanisms, however, are also involved in the development of physical dependence [29–32], placing premorbid behavior, dependence, and addiction to a substantial degree on the same dimension.

Despite the pathogenetic heterogeneity of addictions, both a single common (non-drug-specific) liability dimension and the feasibility of its measurement are supported by clinical, neurobiological, genetic, and statistical findings [7, 32–34]. Substance-specific mechanisms of metabolism and neurobiology notwithstanding, substantial commonality exist among the different substance use disorder categories. Addiction to illicit drugs and alcohol is strongly associated with behavior dysregulation (disinhibition) and antisociality. These associations and other commonalities between the liabilities to drug-specific SUDs suggest common sources of variation, termed *general/common liability to addiction*, GLA [32, 35, 36]. High phenotypic and genetic correlations between substance-specific addiction liabilities, as well as correlations of those liabilities with externalizing/antisocial characteristics [37], point to the mechanisms of behavior regulation and socialization as possible sources of commonalities. Although neurobiological mechanisms of drug response, obviously, do not form distinct groups related to the legality of substances, genetic correlations between dependence symptoms indicate two distinct albeit correlated sources of genetic variance for licit and illicit substances [38]. These *genetic* differences are likely due to an *environmental* factor, viz., the barrier of illegality that needs to be overcome for prodromal involvement with illegal drugs.

Addiction develops in response to an environmental agent, as does PKU, but prodromal exposure to drugs is usually a voluntary choice (prescription medication is an exception). The PKU phenotype is defective metabolically, via the toxic effect of phenylpyruvate at the cell level, in contrast to the behavioral phenotypic level at which the genetic predisposition to addiction is realized—with no true premorbid metabolic defect to attribute that pathological phenotype to. In fact, the virtually only known addiction-related metabolic “defect,” ALDH2 deficiency, is protective against exposure and thus addiction to alcohol.

Addictive substances are ubiquitous but are not as universally consumed as food (with alcohol's status less categorically defined due to its traditional role as a food staple). The decisive role of individual behavioral choice renders the supply-side law enforcement measures, involving enormous resources and effort, less than successful in risk reduction. Where a decline in incidence is observed (e.g., crack-cocaine smoking), no particular agency can lay claim to that success [39]. A particularly positive example pertaining to addictive substances is the decrease in addiction to tobacco. It has declined by 50 % since 1965—though not through the direct control of nicotine consumption, limited mostly to restrictions on smoking in public areas. Along with the latter's possible influence on social acceptability of smoking, the *perception* of its “coolness” as a symbol of adulthood, independence or manliness, and camaraderie, a risk factor, has diminished. In parallel, the perception of smoking's “uncool” aspects³ and harm, i.e., in individual *resistance* to this environmental factor's pressure, has grown. Whereas for a child the ability to smoke signifies independence (from the social norms regulating childhood behavior), the situation is reversed for an adult smoker—exactly because of dependence, the inability to part with a characteristic that is supposedly voluntary and no longer attractive or even common in the mainstream society. Moreover, the characteristics that have been previously ignored—the smell, the morbidity, the social status, and intelligence of the smoker—may influence children as well and offset any remaining coolness. The marginalization of smoking is supported by its increased association with psychopathology [41]. According to the

³ This also implies a possibility of reversal of the positive trend—if smoking's “coolness” is reestablished. Growth in hookah-smoking [40] illustrates this point. The reinstatement of the “cool” status is also possible via a role model's using tobacco. Legalization of cannabis, the euphoriant effects of which, rather than other factors as for tobacco (symbolism of adulthood, masculinity, etc.) determine its appeal, may also diminish the repellent effects of the act of smoking that have been somewhat established for tobacco, especially when both substances are mixed in a cigarette. That could finally render cannabis a “gateway”—for reintroduction of smoking as a mainstream behavior.

Monitoring The Future study, the lifetime prevalence of marijuana use among 12-graders has become higher than that of cigarette smoking, with a growing gap (45.5 vs. 40.0 % in 2012; 44.4 vs. 34.4 % in 2014) [42, 43]. This is paralleled by the shift in attitudes toward marijuana, with the majority of Americans polled in 2013 favoring legalization [44], and its legalization in several states.

Legal repercussions and demonstrable harm to personal health and social status have not been sufficient to reach a satisfactory decrease in the prevalence of addiction to illicit drugs, which remains high. The “coolness” factor and thus the potential benefit of this risk factor's neutralization are of limited applicability to illicit drugs and alcohol abuse. In contrast to the swashbuckling cowboys of tobacco advertisements, the image of a drug addict or an inebriated person has hardly ever been positive in the public consciousness—even in subcultures where drug use and problem drinking are virtually normative. In contrast to tobacco, the subjective attractiveness of illicit drugs and alcohol is mostly not in symbolism and a mild relaxation and concentration gain, but rather in the more dramatic pharmacologic, including euphoriant, effects. Reinforcement—both positive and negative—due to the drugs grouped as illicit could be subjectively stronger than for tobacco and alcohol (which again takes a less defined position). It is frequently the rewarding experience and the neglect of the societal (at least, macrosocial) behavioral norms that drives one's continued consumption of a drug—at least until physiological dependence comes into play as well. The consequences and perception of those norms may vary by age, socioeconomic level/group, and/or access to social support, potentially resulting in variation in pathogenesis and the rate and mechanisms of recovery.

The relatively high societal barrier with regard to persistent drug use is one likely reason why liability to drug addiction shares a large portion of variance, including genetic, with antisociality. Accordingly, it clusters with liabilities to disruptive behavior and antisocial personality disorders [37], as well as with behavior dysregulation/disinhibition [45], leading to the conceptualization of addiction as part of the externalizing spectrum [46]. These characteristics combine with affect change and other incentives for drug use. Euphoria may have evolved as an indicator of the positive Darwinian value of an experience, but it is possible that the true indicator of a Darwinian fitness-significant behavior is any positive affect change rather than necessarily euphoria [31]. Norm violation and rebelliousness, elevated novelty-seeking and risk-taking, are common features of adolescence [47], especially when exacerbated by maturational mistiming [48]. They may be additional stimuli for drug consumption, often initiated in adolescence. It is noteworthy that parental SUD is related to faster sexual maturation in offspring, associated, in turn, with higher peer deviance and elevated SUD risk [49, 50]. Upon

development of physical dependence, these factors are augmented by craving and withdrawal, which frequently leads to further behavioral deviance.

This suggests that focusing research on, and the removal of, risk factors—such as by restricting access to substances or to their hedonic effects—is unlikely to be sufficiently fruitful. Access restriction, the “war on drugs,” has been of limited effectiveness. Influencing hedonic effects has so far been largely limited to methadone replacement for opiate addiction, a type of therapy that is less applicable to other drugs (bupropion or varenicline in smoking cessation is an analogy). Blocking drug reward as such and other effects at the neurochemical level obviously cannot be neutral from the standpoint of neural system functioning, is likely to affect the natural reward mechanisms, and thus is not the optimal approach.

Neither would the concept of resilience—at least defined as referred above—be fully satisfactory as a guide for effective intervention. For instance, for addiction, even if resilience is defined specifically for this disorder, it would imply the return to the pre-“stress” condition that may be unreachable for addicts—due to drug effects on mechanisms of neural plasticity that may involve irreversible subcellular level changes. It is possible, but has yet to be tested, that remission and/or recovery from addiction (i.e., compulsive behavior) can occur without the brain systems’ return to their predependence state or a substantial degree thereof. This does not mean that recovery from addiction as compulsive *behavior* is not possible. It means, however, that the recovery mechanisms—spontaneously or consciously activated resistance—could be located immediately at the behavioral rather than physiologic level (with possible subsequent alleviation of physiological manifestations). As noted, the measures that may offset the risk or help treatment by increasing resistance are not necessarily the obverse of the factors that contribute to increased risk. For instance, whereas a person’s drug involvement could have been facilitated by a combination of access to drugs, peers’ encouragement, and pleasurable effects, its discontinuation could have resulted from recognition of developing compulsion and the timely exercise of volitional cognitive control. A case in point is provided by Richard Feynman, a Nobel laureate in physics, who stopped drinking alcohol upon noticing that it was becoming involuntary—because he felt that it would be threatening the pleasure he derived from his thinking [51]. Tellingly, among individuals exposed to chronic opioid analgesic therapy (COAT), less than 0.1 % becomes addicted *de novo*, while overall illicit drug use among COAT patients does not exceed its prevalence in the general population [52].

To elucidate the resistance approach, viruses present a fitting analogy to addictive substances. It is hardly feasible to remove these substances from the environment and thus preclude exposure—similarly, it is not feasible to directly remove viruses. Moreover, both viruses and drugs mutate, in addition to difficulties in fighting the current varieties. Raising *resistance* to

viruses, however, is a method of choice for diseases like polio, smallpox, rabies, or influenza. It was the observation of resistance (immunity) that allowed Edward Jenner (and others [53]) to translate the “literature” (the tales about dairymaids who were resistant to smallpox after suffering from more benign cowpox) into the treatment. The discovery of vaccination, which would eventually bring about the eradication of smallpox, long preceded the knowledge of the main cause of the disease.

This analogy also illustrates the resistance/health-oriented sampling approach. It was the identification of a high-*resistance* population, the immune dairymaids, which enabled the identification of the resistance-increasing factor, a vaccine, just as the observation of the affected population (risk/disease-oriented approach) would enable the discovery of the virus, the risk factor. Likewise, the resistance effect of a “defective” ALDH2 allele (ALHD2*2) was found in the relatively highly alcoholism-resistant population of East Asians [54]. It could not be observed in Caucasians, in whom this allele is absent—an example of the asymmetry of the risk-oriented and resistance-oriented approaches. Dealing with the pathogen is appropriate in some cases (e.g., antiretroviral therapy for HIV; antibiotics for bacteria). Such an approach, however, may not be feasible or effective in many other cases, whereas raising resistance to the pathogen (and search for resistance factors) may be more feasible and promising—particularly, in prevention. This is especially relevant to drugs of abuse, a known pathogen, exposure to which is eminently avoidable. Nevertheless, it is the *risk* factors that are more commonly pursued in research, focusing on high-risk and affected groups. The analogy between drugs and viruses is underscored by attempts to develop an actual vaccine treatment for addiction, e.g., cocaine dependence. Obviously, however, such treatment is drug-specific, whereas polydrug use is the norm. The efficacy of that treatment is also still questionable [55].

APPROACHES TO MEASUREMENT, MECHANISMS, AND PREDICTORS OF RESISTANCE

The implementation of resistance-based research methodology is intrinsically oriented to translation by its focus on health maintenance. It also relies on the lifetime perspective on the phenotype. Ontogenesis is an important characteristic of liabilities to addictions [13] and to many other complex disorders. Every person is born with an initial SUD liability phenotype, determined by the individual genetic, inherited epigenetic, and intrauterine environment background. This phenotype undergoes life-long development dependent on basic ontogenetic changes and the response to environmental stimuli, including exposure to drugs. Environmental factors are subject to increasing influence (and thus confounding) by the phenotype at a prior time point, and ultimately by the genotype. This results in genotype-environment correlations—from passive (referring to early environment

as influenced by heritable parental characteristics) to reactive/evocative (referring to the environment's response to heritable individual behavior) to active, as the individual seeks the environment that fits the behavioral phenotype and hence ultimately the genotype [56, 57], including epigenetic gene expression changes in response to the environment (e.g., [58]). In effect, this renders the environment part of the extended phenotype.

Both organismic and environmental factors at the individual level can be viewed as vectors of force. The resultant vector at any time point determines the direction of the individual ontogenetic *trajectory* of the liability phenotype—toward or from the suprathreshold portion of the liability scale [59]—calling for longitudinal observations. The variety of individual trajectories likely represents a continuum [60], as it derives from continuous liability distributions at each time point, with additional migrations of the labile individual phenotype over time on the liability scale. *Selecting appropriate samples may allow identification of a subset of trajectories that characterizes highly resistant individuals*, as well as consideration of various facets of resistance.

The resistance perspective upends the usual case-control paradigm into designs that involve sampling individuals who are at the low end of the respective liability scale, possessing high resistance phenotypes as defined by a health-significant target, e.g., SUD. Such targets may include but are not necessarily limited to (1) high estimated outset resistance, (2) high realized resistance (high estimated childhood behavioral risk for a disorder combined with healthy adult outcome), (3) resistance to continued drug use after initiation, (4) resistance to addiction after a substantial period of continuous consumption, (5) ability to recover despite becoming addicted—whether under treatment or independent of it (the recovery rates are known to be comparable [61], in both cases likely heavily dependent on the individual's commitment to quitting), including “maturing-out” of addiction as manifestation of resistance to chronicity, and (6) resistance to relapse—maintenance of recovery from addiction. Each of these targets obviously presents its own requirements for comparison groups and phenotyping rather than a common case-control division in risk-oriented research. To illustrate practical application of the resistance perspective in addiction research, we will consider the high outset and high realized resistance targets.

As noted, one of the main difficulties in the implementation of the resistance-oriented paradigm is the measurement of “normality.” In the absence of the face-valid indicators of resistance, capable of discriminating between resistance phenotypes in the asymptomatic individuals or in childhood, novel tools are needed to enable the identification of high resistance individuals, the group(s) wherein the resistance factors are likely to be aggregated and thus discoverable. An opportunity for that is afforded by the combination of continuous liability indices such as Transmissible

Liability Index (TLI) [33], a validated childhood measure of adult liability to addiction, and the longitudinal data—from childhood to an adult clinical outcome. Briefly, transmissible liability is the component of phenotypic variance that is correlated between generations, via genetic and/or environmental mechanisms, based on the model partitioning liability variance into two components, transmissible and nontransmissible [62, 63]. Inasmuch as SUD liability is transmissible (at least because of its significant heritability), children's characteristics that discriminate between groups with affected and unaffected parents are likely to be indicators of children's transmissible SUD liability [7]. Using these indicators, liability is quantifiable, e.g., by item response theory (IRT) methods. In particular, the TLI scale is based on 45 items related to childhood indicators of behavior regulation [33].

The critical step is to identify indicators specifically of resistance to addiction, i.e., to relate the psychological indicators to the latent trait of resistance to addiction. Such indicators can be selected based on their *ability to discriminate between the control and high resistance groups*. This would form the foundation for resistance to be the (dominant) dimension shared in common between the indicators, establishing the essential unidimensionality of the item set for IRT analysis. Consistent with addiction's being a behavioral phenotype, these indicator variables should be selected from among the items comprising instruments assessing the psychological domain (the psychological tools for the study should be selected to cover not only behavioral deviance but normal psychology as well, to minimize measurement error in the normality area). The contrasts pertain to two types of criteria for ascertaining the resistance phenotype: by measured outset resistance (e.g., at age ~10) and by realized liability (at adulthood). The combination of these two types of ascertainment allows for the identification of individuals who had low liability as children (high outset resistance) or had high liability that was offset during subsequent development (high realized resistance). Accordingly, two alternative indices of resistance can be derived using this combination of criteria: (1) pertaining to high outset resistance (*HOR*; those who had low TLI at baseline *and* have not developed an SUD by adulthood) and (2) pertaining to high realized resistance (*HRR*; those who had high TLI at baseline *but* have not developed SUD by adulthood). Low and high outset liability can be defined, respectively, as *below* and *above* certain low and high percentiles on the TLI scale, in accordance with a reasonable compromise between the theoretically advantageous selection of extreme phenotypes and the sample size requirements for meaningful analyses. The *HOR* group is likely to be enriched with factors determining *low outset liability*, while the *HRR* group, with factors *capable of offsetting high outset liability during subsequent development*.

It is important to identify the appropriate control group to maximize the informativeness of the contrasts. The control group can be defined as the rest of

the unaffected sample—i.e., with TLI phenotypes *between* the above defined low and high percentiles. The reason why the *affected* (i.e., low realized resistance) individuals are *excluded* from the control sample is that there is aggregation of high-risk factors among these individuals (see Fig. 1). Because of the relative diagnostic certainty as compared with the more probabilistic definition of the high-resistance phenotype, the results of comparisons with the sample including affected individuals would be likely driven by high-risk rather than high-resistance factors. Removing those individuals from comparisons renders the average liability of the control close to the population mean and lowers the impact of risk factors. The control group can thus be designated average resistance (*AR*). The items selected via the respective contrasts will thus be related to aggregated resistance, rather than risk, factors. Upon selecting indicators of resistance in this fashion and deriving the resistance constructs, the entire sample can then be scored on them and used for longitudinal modeling of these two facets (or alternative definitions) of resistance. Such scoring would afford an equal treatment of liability phenotypes along the trait scale.

To derive a resistance scale, the selected items can then undergo factor analyses to ensure the unidimensionality of the item set, followed by IRT analysis to calibrate the items as indicators of a resistance construct. A graded response IRT model [64] can be applied to such mixed-format item response sets (with various numbers of response categories). A data-fitting IRT model has features that are uniquely valuable for trait measurement and harmonization of data across studies: (1) Item parameters are invariant of the sample, and (2) trait estimates are invariant of items used, allowing different item sets to be applied while maintaining a common scale, enabling adaptive measurement, also known as tailored testing [65]. In turn, these constructs enable tracking developmental trajectories of resistance to addiction, identifying those related to high resistance.

Finally, to fully benefit from the resistance approach, an important analysis element is testing the associations of the putative mechanistic factors with liability defined from the resistance perspective. These factors include organismic (genetic, biochemical, and physiological) as well as environmental characteristics. The tests are to evaluate their relationship with parameters of the resistance developmental trajectories (e.g., intercept and slope in latent growth mixture modeling, with the diagnostic outcome as the indicator of latent class) but can also include direct comparisons between the high (HRR and HOR) and average (AR) resistance groups, or other association-testing methods.

Similar approaches, using appropriate sampling designs, can be applied to the other facets of resistance, as well as to liability to any other disorder. Outset liability indices can be created with selecting items by referencing them to the children's own phenotype as adults, if longitudinal data are available—instead of

relying on the indicators of the transmissible liability component by referring children's characteristics to parental outcomes as in TLI.

CONCLUSIONS

This article delineates a novel conceptualization of translation-oriented biomedical research, which redirects attention from factors elevating risk and leading to disease (risk factors) to the factors associated with minimization of disease probability and severity (resistance factors). The resistance concept subsumes, but is not limited to, resilience and protective factors, covering also organismic and environmental factors that preclude exposure to a pathogen (e.g., addictive substances), preclude disorder development despite high estimated risk, facilitate recovery upon disorder, prevent relapse, etc. The reversal of the research perspective requires substantial changes in approaches to phenotypic measurement and sampling, discussed in the paper. The paper's focus thus pertains to the foundational T0 type translation research (Table 1). Focusing on malleable *resistance* factors may facilitate reaching the goal of maintaining and perfecting health, as well as fighting disease, providing results immediately amenable to the T1 type translation. Employed in intervention development, these factors are likely to have the highest impact and translation potential in maintaining or leading to health, as opposed to risk factors whose effects are to be neutralized or reversed—frequently a difficult task. Detecting resistance factors requires identification of low liability (high resistance) individuals, which is not afforded by the common disease-oriented schemata that target high-risk/affected individuals. The article presents a methodological framework that implements the resistance research perspective.

Compliance with ethical standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards: Michael Vanyukov, Ralph Tarter, Kevin Conway, Galina Kirillova, Redonna Chandler, and Dennis Daley declare that they have no conflict of interest. All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national).

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1. WHO. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19–22 June, 1946; signed on 22 July 1946 by the representatives of 61 States and entered into force on 7 April 1948. International Health Conference; April 7, 1948, 1948; New York.
2. Johns LC, van Os J. The continuity of psychotic experiences in the general population. *Clin Psychol Rev*. 2001; 21(8): 1125–1141.
3. NIMH. NIMH Research Domain Criteria (RDoC). 2011; <http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml>. Accessed December 6, 2014.
4. Insel T. Director's Blog: Transforming Diagnosis. 2013; <http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml>. Accessed April 29, 2013.
5. Fulford KW, Bortolotti L, Broome M. Taking the long view: an emerging framework for translational psychiatric science. *World Psychiatr : Off J World Psychiatr Assoc*. 2014; 13(2): 110–117.

6. Alberts B, Kirschner MW, Tilghman S, Varmus H. Rescuing US biomedical research from its systemic flaws. *Proc Natl Acad Sci U S A*. 2014; 111(16): 5773-5777.
7. Vanyukov MM, Kirisci L, Tarter RE, et al. Liability to substance use disorders: 2. A measurement approach. *Neurosci Biobehav Rev*. 2003; 27(6): 517-526.
8. O'Brien CP, Volkow N, Li TK. What's in a word? Addiction versus dependence in DSM-V. *Am J Psychiatry*. 2006; 163(5): 764-765.
9. Falconer DS. The inheritance of liability to certain diseases, estimated from the incidence among relatives. *Ann Hum Genet*. 1965; 29: 51-76.
10. Bucholz KK, Heath AC, Reich T, et al. Can we subtype alcoholism? A latent class analysis of data from relatives of alcoholics in a multi-center family study of alcoholism. *Alcohol Clin Exp Res*. 1996; 20(8): 1462-1471.
11. Neale MC, Cardon L. Methodology for Genetic Studies of Twins and Families. Dordrecht: Kluwer Academic Publishers; 1992.
12. Reich T, Cloninger CR, Guze SB. The multifactorial model of disease transmission: I. Description of the model and its use in psychiatry. *Br J Psychiatr*. 1975; 127: 1-10.
13. Tarter RE, Vanyukov M. Alcoholism: a developmental disorder. *J Consult Clin Psychol*. 1994; 62(6): 1096-1107.
14. Clayton RR. Transitions in drug use: Risk and protective factors. In: Glantz MD, Pickens RW, eds. *Vulnerability to Drug Abuse*. Washington, DC: American Psychological Association; 1992: 15-51.
15. Kendler KS, Myers J. Addiction resistance: definition, validation and association with mastery. *Drug Alcohol Depend*. 2015.
16. Masten AS, Best KM, Garmezy N. Resilience and development: Contributions from the study of children who overcome adversity. *Dev Psychopathol*. 1990; 2: 425-444.
17. Windle M. Critical conceptual and measurement issues in the study of resilience. In: Glantz MD, Johnson JL, eds. *Resilience and development: positive life adaptations*. New York: Kluwer Academic/Plenum Publishers; 1999: 161-176.
18. Khatzian EJ. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry*. 1985; 142(11): 1259-1264.
19. Wingo AP, Ressler KJ, Bradley B. Resilience characteristics mitigate tendency for harmful alcohol and illicit drug use in adults with a history of childhood abuse: a cross-sectional study of 2024 inner-city men and women. *J Psychiatr Res*. 2014; 51: 93-99.
20. Schulenberg JE, Maggs JL. A developmental perspective on alcohol use and heavy drinking during adolescence and the transition to young adulthood. *J Stud Alcohol Suppl*. 2002; 14: 54-70.
21. Zhong S, Monakhov M, Mok HP, et al. U-shaped relation between plasma oxytocin levels and behavior in the trust game. *PLoS One*. 2012; 7(12): e51095.
22. Steinberg L, Monahan KC. Age differences in resistance to peer influence. *Dev Psychol*. 2007; 43(6): 1531-1543.
23. Spielman RS, McGinnis RE, Ewens WJ. Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am J Hum Genet*. 1993; 52(3): 506-516.
24. Tarter R, Vanyukov M. Re-visiting the validity of the construct of resilience. In: Glantz MD, Johnson JL, eds. *Resilience and development: positive life adaptations*. New York: Plenum Press; 1999: 85-100.
25. Kendler KS, Heath AC, Neale MC, Kessler RC, Eaves LJ. A population-based twin study of alcoholism in women. *JAMA*. 1992; 268(14): 1877-1882.
26. McGue M, Pickens RW, Svikiel DS. Sex and age effects on the inheritance of alcohol problems: a twin study. *J Abnorm Psychol*. 1992; 101(1): 3-17.
27. McCutcheon VV, Grant JD, Heath AC, et al. Environmental influences predominate in remission from alcohol use disorder in young adult twins. *Psychol Med*. 2012; 42(11): 2421-2431.
28. Friend SH, Schadt EE. Translational genomics: clues from the resilient. *Science*. 2014; 344(6187): 970-972.
29. Kreek MJ, Koob GF. Drug dependence: stress and dysregulation of brain reward pathways. *Drug Alcohol Depend*. 1998; 51(1-2): 23-47.
30. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*. 2001; 24(2): 97-129.
31. Vanyukov MM, Tarter RE, Kirillova GP, et al. Common liability to addiction and "gateway hypothesis": theoretical, empirical and evolutionary perspective. *Drug Alcohol Depend*. 2012; 123(Suppl 1): S3-17.
32. Vanyukov MM, Tarter RE, Kirisci L, Kirillova GP, Maher BS, Clark DB. Liability to substance use disorders: 1. Common mechanisms and manifestations. *Neurosci Biobehav Rev*. 2003; 27(6): 507-515.
33. Vanyukov MM, Kirisci L, Moss L, et al. Measurement of the risk for substance use disorders: phenotypic and genetic analysis of an index of common liability. *Behav Genet*. 2009; 39(3): 233-244.
34. Schwantes-An TH, Zhang J, Chen LS, et al. Association of the OPRM1 Variant rs1799971 (A118G) with Non-Specific Liability to Substance Dependence in a Collaborative de novo Meta-Analysis of European-Ancestry Cohorts. *Behav Genet*. 2015.
35. Conway KP, Levy J, Vanyukov M, et al. Measuring addiction propensity and severity: the need for a new instrument. *Drug Alcohol Depend*. 2010; 111(1-2): 4-12.
36. Vanyukov MM. Substance-specific symptoms and general liability to addiction. *Am J Psychiatry*. 2012; 169(10): 1016-1018.
37. Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry*. 2003; 60(9): 929-937.
38. 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(11): 1313-1320.
39. Parker MA, Anthony JC. Should anyone be riding to glory on the now-descending limb of the crack-cocaine epidemic curve in the United States? *Drug Alcohol Depend*. 2014; 138: 225-228.
40. Jawad M, McEwen A, McNeill A, Shahab L. To what extent should waterpipe tobacco smoking become a public health priority? *Addiction*. 2013; 108(11): 1873-1884.
41. Talati A, Wickramaratne PJ, Keyes KM, Hasin DS, Levin FR, Weissman MM. Smoking and psychopathology increasingly associated in recent birth cohorts. *Drug Alcohol Depend*. 2013; 133(2): 724-732.
42. Johnston LD, O'Malley PM, Bachman JG, Schulenberg J. Marijuana use continues to rise among U.S. teens, while alcohol use hits historic lows. 2011; <http://www.monitoringthefuture.org>. Accessed April 17, 2012.
43. Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg JE. Monitoring the future national survey results on drug use: 1975-2014: Overview, key findings on adolescent drug use. 2015; <http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2014.pdf>. Accessed October 20, 2015.
44. Jones J, Saad L. Gallup Poll Social Series: Crime 2015; http://www.gallup.com/file/poll/165545/Views_on_Legalizing_Marijuana_131022.pdf. Accessed February 17, 2015.
45. Iacono WG, Malone SM, McGue M. Behavioral disinhibition and the development of early-onset addiction: common and specific influences. *Annu Rev Clin Psychol*. 2008; 4: 325-348.
46. Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. *J Abnorm Psychol*. 2002; 111(3): 411-424.
47. Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev*. 2000; 24(4): 417-463.
48. Tarter R, Vanyukov M, Giancola P, et al. Etiology of early age onset substance use disorder: a maturational perspective. *Dev Psychopathol*. 1999; 11(4): 657-683.
49. Kirillova GP, Vanyukov MM, Kirisci L, Reynolds M. Physical maturation, peer environment, and the ontogenesis of substance use disorders. *Psychiatry Res*. 2008; 158(1): 43-53.
50. Kirillova G, Reynolds M, Kirisci L, et al. Familiality of addiction and its developmental mechanisms in girls. *Drug Alcohol Depend*. 2014; 143: 213-218.
51. Feynman RP. "Surely You're Joking, Mr. Feynman!" *Adventures of a Curious Character*. New York: W. W. Norton and Company; 1985.
52. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? a structured evidence-based review. *Pain Med*. 2008; 9(4): 444-459.
53. Riedel S. Edward Jenner and the history of smallpox and vaccination. *Proc (Bayl Univ Med Cent)*. 2005; 18(1): 21-25.
54. Harada S, Agarwal DP, Goedde HW. Aldehyde dehydrogenase polymorphism and alcohol metabolism in alcoholics. *Alcohol*. 1985; 2(3): 391-392.
55. Kosten TR, Domingo CB, Shorter D, et al. Vaccine for cocaine dependence: a randomized double-blind placebo-controlled efficacy trial. *Drug Alcohol Depend*. 2014; 140: 42-47.
56. Plomin R, DeFries JC, Loehlin JC. Genotype-environment interaction and correlation in the analysis of human behavior. *Psychol Bull*. 1977; 84(2): 309-322.
57. Scarr S, McCartney K. How people make their own environments: a theory of genotype greater than environment effects. *Child Dev*. 1983; 54(2): 424-435.
58. Massart R, Bamea R, Dikshtein Y, et al. Role of DNA methylation in the nucleus accumbens in incubation of cocaine craving. *J Neurosci*. 2015; 35(21): 8042-8058.
59. Vanyukov MM, Tarter RE. Genetic studies of substance abuse. *Drug Alcohol Depend*. 2000; 59(2): 101-123.
60. Lahey BB, Waldman ID. A developmental model of the propensity to offend during childhood and adolescence. In: Farrington DP, ed. *Integrated Developmental and Life-Course Theories of Offending (Advances in Criminological Theory)*. New Brunswick: Transaction Publishers; 2005: 15-50.

61. Moos RH. Treated or untreated, an addiction is not an island unto itself. *Addiction*. 1994; 89(5): 507-509.
62. Vanyukov M, Moss H, Tarter R. Research designs in family studies. In: Sloboda Z, Bukowski WJ, eds. *Handbook of drug abuse prevention: theory science and practice*. New York: Kluwer Academic/Plenum Publishers; 2003: 497-519.
63. Rice J, Cloninger CR, Reich T. General causal models for sex differences in the familial transmission of multifactorial traits: an application to human spatial visualizing ability. *Soc Biol*. 1980; 27(1): 36-47.
64. Samejima F. Estimation of ability using a response pattern of graded scores. 1969.
65. Reckase MD. A procedure for decision making using tailored testing. In: Weiss DW, ed. *New horizons in testing: latent trait test theory and computerized adaptive testing*. New York: Academic; 1983: 238-255.