Application of environmental sensitivity theories in personalized prevention for youth substance abuse: a transdisciplinary translational perspective

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Abstract

Preventive interventions that target high-risk youth, via one-size-fits-all approaches, have demonstrated modest effects in reducing rates of substance use. Recently, substance use researchers have recommended personalized intervention strategies. Central to these approaches is matching preventatives to characteristics of an individual that have been shown to predict outcomes. One compelling body of literature on person $\times$ environment interactions is that of environmental sensitivity theories, including differential susceptibility theory and vantage sensitivity. Recent experimental evidence has demonstrated that environmental sensitivity (ES) factors moderate substance abuse outcomes. We propose that ES factors may augment current personalization strategies such as matching based on risk factors/severity of problem behaviors (risk severity (RS)). Specifically, individuals most sensitive to environmental influence may be those most responsive to intervention in general and thus need only a brief-type or lower-intensity program to show gains, while those least sensitive may require more comprehensive or intensive programming for optimal responsiveness. We provide an example from ongoing research to illustrate how ES factors can be incorporated into prevention trials aimed at high-risk adolescents.

Keywords

Substance use, Prevention, Environmental sensitivity, Risk severity, Differential susceptibility, Personalization

Alcohol and other drug use among adolescents is a serious public health concern in the USA. For example, by late adolescence, over 78 % of teens will have experimented with alcohol, over 47 % will be engaged in regular drinking habits, and over 14 % will have met criteria for lifetime abuse [1]. Despite herculean efforts over the previous five decades to stem the rising tide of substance use, treatment approaches (largely based on behavioral parent training and cognitive behavioral therapy principles) have been modest at best; there is considerable variability in outcomes, and no one model works similarly for all youth [2]. Even among those who experience initial success following treatment, relapse rates are high [3].

Implications

Practitioner: Measuring environmental sensitivity as a moderator of intervention response may lead to the development of a screening tool that prevention practitioners can use to tailor the type or dosage of preventatives to their high-risk clients.

Policy Maker: Personalized preventive interventions informed by indices of environmental sensitivity may increase the efficiency of interventions, minimize burden, and reduce costs, all of which have important implications for policy.

Researcher: Researchers are encouraged to incorporate indices of environmental sensitivity into ongoing prevention research to explore novel, innovative, translational-informed moderation effects.

Prevention approaches offer more promise as they target risk factors before they become fully crystallized and, as a result, may work to preempt risk trajectories leading to chronic use, abuse, and addiction. The prototype for prevention has been a universal approach in which all members of the general population receive programming regardless of their degree of risk. In recent years, more targeted prevention approaches have been defined—selective and indicated [4]. Indicated prevention, for example, targets “high-risk” individuals who are at the early stage of problem development but have not yet been diagnosed with a substance use disorder. Conventional wisdom would suggest that indicated youth are extremely important, as they have the highest probability of progression to more serious patterns of use, abuse, and addiction. Deflecting these youth off their risky trajectories with effective indicated programming could thus reduce escalation and progression. Despite the intuitive appeal of indicated prevention, it is in its nascent stage and more needs to be learned about how such programs should be designed and presented to high-risk youth and their families.

The current list of evidence-based drug abuse preventive interventions for high-risk youth (e.g., Project Towards No Drug Abuse; Reconnecting Youth Program; Adolescent Transitions Program) is largely indicated and designed as fixed programs that offer uniform composition, dosage, and duration to all participants (“one size fits all”) [5–7]. Unfortunately, programs of this ilk are often costly to deliver, participation and completion rates are generally poor, and modest effect sizes have been reported on key outcomes with considerable variability in individual response [8]. To address these limitations, some prevention scientists have called for “personalized” approaches [9–13]. Personalized health care (i.e., personalized medicine, precision medicine) uses an individual’s unique characteristics (genetic profiles, biomarkers, environmental exposures) to make decisions regarding the best intervention strategy for an individual [14]. Personalized health care is of growing interest, having produced notable successes in oncology, cardiology, and infectious diseases and, most recently, in the treatment of problematic alcohol use in adolescents and adults [14–16]. The fundamental building block of personalized health care is the identification of moderators (i.e., individual difference characteristics), which predict differential response to various preventive intervention options. Once identified, these moderators may be translated into empirically derived decision rules that form the basis for assigning the appropriate dose or type of preventative to each person, based on the person’s values on the moderators (i.e., tailoring variables). This approach would more effectively address the causal heterogeneity among at-risk populations and the response variability that results from “one-size-fits-all”-type prevention.

Emerging advances in translational science provide informative guidelines for the identification of candidate moderators. In the health professions, the term “translational science” has been used to reference a multi-phased process by which research-generated knowledge directly or indirectly relevant to health outcomes serves the general public [17]. As highlighted in this *special edition*, one typology for translational research features five basic stages (see Table 1).

Each stage describes how knowledge gleaned at that stage informs activities at the subsequent stage along a translational pathway extending from “basic science to service.” For example, T0 and T1 may show how new knowledge in the basic sciences about how the causes of disorder and wellness translate to the identification of putative mechanisms of therapeutic action that might serve as targets for an intervention (e.g., teaching youth reflective decision-making skills). At stage T2, these intervention targets are formulated as intervention strategies (programs), which are tested under rigorously controlled conditions to determine the size of their effects (efficacy trials). Once these programs are validated, the translation process moves to stage T3 where programs are tested in community settings to determine if their effects can be replicated under real-world conditions for implementation (effectiveness trials). At stage T4, the goal is wide-scale dissemination where the programs can be evaluated for successful adoption, implementation, institutionalization, and sustainability (scaling-up trials). The translational process culminates when program effects are incorporated into policies for system reform that lead to significant public health impact across different populations and contexts (global communities).

Critical to the translational pathway are iterative feedback loops at each stage whereby knowledge learned at a particular stage can be used to revise and/or refine products of previous stages (back-translation). For example, finding high variability in intervention outcomes among participants during a T2 efficacy trial may suggest a return to T1 to search for alternative risk factors. The existence of alternative risk factors will suggest new behavioral change strategies that will, in turn, inform development of personalized preventive intervention options.

In the present article, we provide an example of a research framework (*personalized, precision-based prevention*) that illustrates the process of back-translation at the interface of stages T1 and T2. This research takes flight from efficacy studies where fixed-type interventions (i.e., non-personalized prevention programs) have yielded considerable variability in intervention response among individuals. This approach requires identification of intervention moderators using a

Table 1 | Translational research stages

Type	Type 0 translation (T0)	Type 1 translation (T1)	Type 2 translation (T2)
Definition	The fundamental process of translating findings and discoveries from social, behavioral, and biomedical sciences into research applied to prevention intervention.	Moving from bench to bedside. Translation of applied theory to methods and program development.	Moving from bedside to practice and involves translation of program development to implementation.
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.

multiple-levels-of-analysis strategy including genes, neural circuits, hormones, cognitions, and behaviors, as well as contextual factors. Testing moderation across multiple levels of analysis may not only provide clues to who responds best to a given intervention but also may facilitate discovery of the pathway to change from genes to behavior that can reveal new targets that increase the precision of prevention efforts.

Unfortunately, much of the existing literature addressing substance abuse has focused on treatment interventions and only a few studies that have examined moderation in preventive interventions (e.g., Fast Track Prevention Program) [18].

Historically, efforts to identify tailoring strategies in the drug abuse treatment field have been largely based on clinically based risk factors (i.e., family history of drug abuse, comorbid mental health problems, cognitive deficits, severity of substance use, etc.). We refer to this mode of moderation as the risk severity (RS) model. Not surprisingly, youth showing greater severity in risk would be matched to more intensive types of intervention. However, this tailoring strategy has produced mixed findings [18]. Project Matching Alcohol Treatment to Client Heterogeneity (MATCH), a multisite clinical trial found little support to show that aspects of RS (e.g., degree of alcohol involvement, psychiatric comorbidity) influenced response to three standard interventions [19]. Similarly, alcohol use prevention programs tailored to adolescents with high levels of risk including those involved in Greek college life or who have a history of family alcoholism have been largely ineffective [20]. Collectively, these findings suggest that investigators look elsewhere for informative moderators of prevention response. It is possible that other moderation models may be more informative or may complement the more traditional RS moderation model. RS factors may be too distal or unrelated to the root causes of prevention non-response, and thus, the search of an alternative model may include factors in closer proximity to the causes of substance use.

In our search for candidate moderators, we were informed by a meta-framework of perspectives on inter-individual variability in perceiving, processing, and responding to contextual factors referred to as *environmental sensitivity* (ES) [21]. Five distinct but related frameworks comprise ES, including *diathesis stress*, *differential susceptibility theory* (DST), *sensory processing sensitivity* (SPS) [22], *biological sensitivity to context* (BSC) [23], and *vantage sensitivity* (VS) [24]. Readers of this journal may be most familiar with the dominating diathesis stress model [25], which focuses on how individuals vary in terms of their vulnerability to problem behaviors in the face of adversity. More recently, additional models have emphasized the fact that people may be more or less sensitive to, not only disadvantaged environments, but also enriched environments as well [23, 24]. This specific differential sensitivity to supportive contexts is central to our prevention framework. Briefly, we outline each concept. Based on data from numerous studies, the central tenet

of DST emerged—in many cases, individuals most susceptible to the damaging effects of adverse and stressful environmental contexts appear to display similar degrees of sensitivity to positive and supportive contexts in the form of developmentally adaptive behaviors [26]. Individual differences in this “for better or for worse” sensitivity to context exist and appear to be predicted by factors across multiple levels of analysis [27–29]. The concept of VS has been proposed by Pluess and Belsky [24] and is similar but distinguished from DST with regard to the environmental range considered. Vantage sensitivity refers to the varying degree to which individuals benefit specifically from supportive environments, as opposed to describing sensitivity across the full environmental spectrum. Vantage sensitivity factors promote beneficial outcomes while vantage-resistant factors inhibit or make it more difficult to benefit from positive contexts. SPS is a personality-based perspective proposed by Aron and Aron [22] wherein individuals differ in terms of their cognitive processing of environmental influence, attention to sensory information, and inhibited behaviors. Measures of SPS have been examined as intervention moderators [24]. Finally, BSC theory describes inter-individual variation in bio-behavioral reactivity to both positive and negative environments with particular focus on how the environment itself, in addition to genetics, shapes ES [23].

Because the diathesis stress model does not predict differential response to positive environmental influence, such as that embodied in prevention programs, it is not compatible with our prevention framework. However, all other ES perspectives are compatible and we herein refer to factors, across multiple-levels-of-analysis, which predict variability in ES to positive environments as *ES factors*. More specifically, the inclusion of ES factors in prevention trial designs may shed light on variables, which not only explain systematic response heterogeneity but may also possess tailoring utility. Belsky and van IJzendoorn [30] describe the need to “expand the duration, intensity, or range of interventions and thereby determine just how generally or specifically unsusceptible are those who appear not to benefit from interventions being implemented.” Building upon that notion, individuals rated high on ES (possessing a number of ES factors and/or absence of vantage-resistant factors) may respond favorably to brief-type preventive interventions that target a specific skill set or less intense versions of existing preventive interventions that feature only key points of interest. However, individuals rated low on ES (lacking ES factors and/or presence of vantage-resistant factors) may require more comprehensive (targeting multiple risk factors) and/or more intense prevention efforts in order to show the same adequacy of response (see Fig. 1). It is important to note that we would, nevertheless, predict that most youth would respond to more intense preventive interventions, regardless of sensitivity levels. It stands to reason, however, that the lower-intensity preventatives would be preferred to mitigate cost, burden, and possible

Hypothesized Environmental Sensitivity Effects

Fig. 1 | Hypothesized environmental sensitivity effects

iatrogenic effects. We should emphasize that our goal is for youth to reach an optimal level of responsiveness. Inclusion of ES factors, known to predict differential sensitivity to positive environments, into prevention trials may augment more traditional prevention outcome moderators such as risk factors and/or severity of problem behaviors (RS).

EXPERIMENTAL EVIDENCE OF ES

The overwhelming majority of studies examining ES moderation have been correlational/observational in nature. A lack of randomization and environmental manipulation within ES studies may contribute to erroneous conclusions otherwise explained by person-environment correlations and type I error [31, 32]. In an effort to overcome these methodological shortcomings, researchers have taken advantage of intervention/prevention trials, wherein both randomization and environmental manipulation are inherent. The goal of this groundbreaking work appears to be focused on better elucidating the etiology of psychopathology, finding missing heritability, and describing ES phenomena more generally, rather than on directly translating such findings into more tailored, clinical approaches [31–36]. Our prevention framework proposes to advance this experimental work one step further, a translational step, with an eye toward personalized, precision-based prevention. We acknowledge that much of the experimental ES literature is based on treatment interventions rather than prevention programs per se, though we believe that the findings are, nevertheless, quite applicable to prevention science.

In a seminal ES experiment, Velderman et al. [37] found that infant temperamental reactivity, a putative ES factor, moderated outcomes of a brief-type preventive intervention aimed at improving maternal sensitivity and attachment security. Specifically, the intervention was most effective for mothers with highly reactive infants; on the other hand, for mothers with low reactive infants, there was no association between gains in maternal sensitivity and attachment security. Similar specification of intervention effects has been observed using infant irritability and child negative emotionality as ES moderators [38–40]. The same investigators also provided the first data on a genetically informed ES intervention. Bakermans-Kranenburg et al. [33] found that 3-year-old children who carried at least one copy of the DRD4 seven-repeat allele, a widely studied ES factor, were most responsive to a brief video-feedback intervention targeted at improving maternal sensitivity and discipline. Children with the seven-repeat allele showed marked reductions in externalizing behavior at the 1-year follow-up, but interestingly, those lacking any copies of the allele were largely unresponsive to the effects of the intervention.

Concerning substance use prevention specifically, Brody and colleagues have delivered some of the most compelling evidence to date that genetic ES factors moderate response outcomes in at-risk, African-American youth [34, 41–43]. Using a polygenic design with multiple genes known to confer ES, Brody et al. [43] found that carriers of more ES genes were more likely to benefit, in terms of reduced substance use, from the Strong African American Families (SAAF) program for preadolescents and for Teens (SAAF-T). Similar genetic findings, using the Adults in the

Making substance use program, were reported in a recent special edition of *Development and Psychopathology* entitled “What works for whom? Genetic moderation of intervention efficacy” [30, 44]. This special issue also included a meta-analysis of 22 gene $\times$ intervention interaction studies, reporting average effect sizes of $r=0.33$ and $r=0.08$ for carriers of susceptibility genotypes and non-carriers, respectively [45].

In contrast to the above findings, Cicchetti et al. [46] found that variation in two putative ES genes, *DRD4* and *5-HTT*, failed to moderate outcomes for maltreated children assigned to either a child-parent psychotherapy intervention (CPP) or a psychoeducational parenting intervention (PPI). Children, on average, responded regardless of genetic variation. Nevertheless, both intervention modalities were quite intense with sessions lasting throughout a 12-month period. This is in contrast to findings from studies using more circumscribed preventive interventions where differential sensitivity may be more informative with regard to dichotomous outcomes (responder vs nonresponder). In fact, the finding that ES factors seem to play a more revealing role in less intensive and more circumscribed interventions is at the heart of our personalization framework. Those with more ES factors may receive benefit from less intensive and more focal-type programs, whereas those lacking ES factors may not benefit as much. Given this intriguing translational hypothesis, we argue that, in addition to continued basic, experimental ES research, preliminary efforts should be made to test ES phenomena with regard to their direct utility in helping to inform personalization strategies in the prevention of substance abuse and other health-compromising problem behaviors. Similar efforts in psychiatry, dubbed *therapygenetics*, are already underway in treatment-focused as opposed to prevention-focused research [47].

REVIEW OF CANDIDATE ES MODERATING FACTORS

Behavioral and personality factors

Early evidence of ES stemmed from studies of difficult temperament and negative emotionality, demonstrating that such behaviors appeared to be indicators of generalized susceptibility to the environment. Indeed, child negativity has been shown to moderate interventions related to maternal empathy, intrusive maternal behavior, sensitive parenting, and teacher-child conflict [48]. Moreover, Aron and Aron [22] developed the Highly Sensitive Person Scale (HSP Scale), later adapted for children [49], which aims to measure the personality construct of SPS directly. This child-adapted scale has been shown to differentially predict depressive outcomes in a school-based, resilience promotion program, with those most sensitive being most responsive [49].

Physiological factors

A number of studies have shown that indices of increased stress responsiveness, as measured by cortisol reactivity and respiratory sinus arrhythmia (RSA) reactivity, display ES effects [24, 50]. Using mother-reported measures of aggression, Eisenberg et al. [51] followed young children for 36 months and those with moderate to high levels of baseline RSA were least likely to be aggressive at follow-up. Similarly, using experimental data, van De Wiel et al. [52] found that cortisol stress reactivity moderated an antisocial behavior intervention, with those demonstrating the highest preintervention cortisol reactivity responding the best.

Genetic factors

The two most commonly studied ES genetic factors include polymorphisms in the *DRD4* and *SLC6A4* genes, related to dopamine and serotonin functioning, respectively. Both genes have shown to moderate environmental exposures in correlational and experimental studies. Bakermans-Kranenburg and van IJzendoorn [35] revealed via a meta-analysis that genetic variants related to dopamine inefficiency (from genes *DRD4*, *DRD2*, and *DAT*) reliably exhibited ES effects, and some of these variants have been used in preventive intervention studies (see above). A similar meta-analysis evidenced robust ES effects from *5-HTTLPR* (a variant of *SLC6A4*) in Caucasian individuals [53]. Finally, evolving evidence suggests that variants in *MAOA*, *BDNF*, *OXTR*, and *CRHR1* genes also appear to moderate environmental influence/interventions consistent with ES effects [48, 54].

INCLUSION OF AN ES FRAMEWORK IN PERSONALIZED PREVENTION RESEARCH

The use of ES theories has been informative in explaining, in part, the vast developmental outcomes observed across multiple environments from adverse to positively enriched. While others have proposed that ES factors may one day have personalization utility [30, 32], a specific strategy for testing such tailoring value in prevention science has yet to be outlined. Here, we discuss our rationale and methodological approach for including ES factors into novel prevention designs in order to test their utility, reliability, and validity in aiding the personalization of programs aimed at reducing substance use and other problem behaviors among high-risk youth.

Rationale: how can ES factors inform personalized prevention?

As the experimental literature has suggested, the primary advantage of ES factors is their ability to explain *systematic heterogeneity* in preventive intervention outcomes. A key tenet of personalized prevention is the importance of examining processes that illuminate why some youth respond and others fail to respond. We believe, based on the reviewed literature, that

some of the heterogeneity observed in substance use prevention trials is explained by variation in levels of ES in youth. In particular, ES factors which explain differential response to positive contexts, derived from DST, VS, SPS, and BSC theories specifically, are relevant for predicting prevention outcomes. Those showing suboptimal response to substance use prevention programs may be low on ES factors, high on vantage-resistant factors, or some combination. The prevention modality may be ideal in terms of fit between target mechanism and risk mechanism, but inadequate in terms of intensity or comprehensiveness.

ES factors may specifically inform the selection of various preventative options within study designs. A majority of the published studies on experimental ES findings compared a relatively circumscribed (brief in focus or low in intensity, i.e., youth focused vs. family focused) intervention to a no-intervention control condition. Comparing one preventive intervention to a control does not lend well to a personalized prevention agenda, as this type of design does not reveal which alternative prevention options may indeed be beneficial. Thus, it crucial to compare multiple, preventive interventions, which vary not only in terms of their mechanism of change, but in their comprehensiveness or intensity as well. Not all systematic heterogeneity is likely to be due to ES; rather, varied responsiveness is most likely due to an amalgamation of variables including RS, motivational influences, target-risk misfit, and age/gender appropriateness among others. Inclusion of ES moderation analysis into prevention trials should serve an augmentation role, attempting to explain heterogeneity beyond the more traditional variables known to interact with prevention program delivery. Of particular, intrigue may be the interplay of the two different, but possibly complementary frameworks, RS and ES, in predicting substance use prevention outcomes. For example, many substance use preventive interventions target youth who reside in contexts of adversity such as low socioeconomic status communities and stressful households, as well as those exposed to deviant peer influences. DST, for example, would predict that, within such contexts, those showing the greatest problem behaviors are probably those most sensitive to the environment and counter-intuitively most likely to respond to even a modest intervention. Conversely, youth with severe problem behaviors residing in relatively positive backgrounds such as a supportive household with a high socioeconomic status may be less sensitive to the environment and may indeed require a more intensive program.

Research methodology

There are numerous ways in which to incorporate ES factors into personalized prevention designs. Here, we describe an approach to determine which ES factors are informative moderators of intervention response, types of trial designs that best suit ES moderation, and an illustrative example from our own research.

Selection of ES factors

A thorough review of the existing literature on ES factors and phenomena should be conducted before incorporating any factors into a prevention trial. A number of key elements should be considered when choosing factors for inclusion. First and foremost, there should be sufficient reason to believe that a given ES factor will indeed moderate the association between a prevention program and the given outcome of interest based on similar studies with similar population demographics and similar outcome measures. When incorporating a novel ES factor, researchers should have sufficient reason to believe that such an ES factor taps similar, sensitivity phenotypes as other, more established, ES factors do. Secondly, researchers need to consider the feasibility of using a given ES factor with their population of interest. Not all ES factors, published in the correlational and/or experimental literature, are feasible with high-risk prevention populations. Contextual sensitivity, duration of assessments, invasiveness, and cost all need to be accounted for. Finally, researchers who seek to test the tailoring utility of ES factors need to use measures that can be administered within a prevention service context such as a school or counseling clinic.

Despite the need for practical utility, researchers may, nevertheless, opt to employ less practical measures (most of which include biological measures) for several reasons: (a) genetic and other expensive biological measures may shed light on systems of sensitivity in which less expensive and more practical tools could be developed to measure, and (b) if biological ES factors prove to be extremely valid tailoring tools either alone or in combination with non-biological measures, such data may encourage program administrators to consider investing in biological technologies. This is especially true when considering the dramatic decrease in genotyping costs, paired with increased versatility and non-invasiveness of biological technology, though cost-benefit analysis should be conducted. Nevertheless, caution is warranted, particularly with the use of genetics. Genetic tailoring and tailoring of any sort should be rigorously tested and clinically validated before translation to prevention programming. Brody and colleagues [31] suggest that tailoring preventive interventions based on genotype may be impractical, could lead to stigma and discrimination, and may not have a cost-benefit due to the prevention paradox. Moreover, given the high rates of non-replication in the GxE field, researchers should pay extra attention when deciding whether to include genetics, which candidate genes to choose from, and how to address statistical concerns related to GxE [55]. What is clear is that selection of prevention modalities based on genotype is far from being ready for “prime time.” Our suggestion to incorporate genetics into prevention trials, if feasible, is meant to test ES moderation across multiple levels in order to evaluate which level or combinations of levels will be most informative [56]. The incorporation of an interdisciplinary multiple-level perspective (team science

framework) will enable prevention scientists to derive a more precise and comprehensive understanding of the moderators underlying successful and unsuccessful preventive intervention outcomes.

Prevention trial designs

In order to evaluate ES-related phenomena from a personalization perspective, researchers should compare a minimum of two interventions. Depending on the problem under study and the researcher's interest, prevention options may vary in their comprehensive focus (e.g., youth skills training vs. family support vs. neighborhood focused) or dosage (e.g., low- vs high-intensity youth skills training) while keeping the underlying mechanism of change as constant as possible. The most basic design compares two preventive interventions, which vary in terms of dosage, along with a control condition. ES factor levels, such as number of ES genotypes or rating on a sensitivity personality scale, and problem behaviors would be measured at preintervention, followed by randomization into one of the three conditions. At follow-up after the prevention program, behavior problems would again be measured as an outcome. A dichotomous responder/non-responder cutoff would be derived based on a desired level of reduced problem behaviors. According to ES hypotheses, the high-intensity (dosage) preventative would produce more responders of both high and low ES, whilst the low-dosage preventative would tend to produce responders who are primarily composed of those most sensitive to the environment.

Non-random assignment such as stratification designs may also be quite revealing. Individuals could be stratified into interventions, which vary along any one of the environmental dimensions that we listed, based on levels of ES factors and/or vantage-resistant factors (i.e., highly sensitive individuals into less comprehensive intervention; less sensitive individuals into more comprehensive intervention). In line with ES theories, such stratified designs would be hypothesized to produce more "responders" than randomization alone. Finally, microtrials and nanotrials, which are smaller in scale and more targeted modalities, may be particularly useful as they are hypothesized to bring about more prominent ES effects [57, 58].

Research example in youth substance abuse prevention

Our research team at the University of Minnesota has initiated a research project with the goal to identify candidate moderators of two evidence-based preventive interventions that seek to preempt the progression of youth substance from mild/moderate to severe levels. This research is aimed at adolescents (ages 13–16) referred to a counseling center by parents, school officials, or law enforcement because of a recent drug use incident. The study uses an augmentation design wherein we aim to evaluate the added value of ES factors in explaining outcome heterogeneity above and beyond the more traditional RS framework. Participants are randomized to one of two prevention

conditions that seek to promote the development of reflective decision-making. These preventions differ, however, in their comprehensive focus, that is, the extent to which they engage more inclusive environmental support. One preventive intervention is the Teen Intervene (TI) program [59], an eight-session youth-focused intervention that uses motivational interviewing, goal setting, and skills training. Motivational interviewing strives to boost the youth's problem recognition and interest in behavioral change by raising awareness of the problem and placing responsibility for change with the youth. Goal setting uses negotiation to encourage youth to adopt prosocial goals. Skills training fosters the development of responsible decision-making with the goal of choosing attitudes and behaviors that are healthier alternative to drug use. As such, TI primarily targets change processes within the youth with only minimal attention given to external environment influence such as family factors. The second preventive intervention is Everyday Parenting (EP) [60], an eight-session family-focused intervention that educates and trains parents to prompt and reinforce self-regulation and decision-making in youth through ongoing parent-youth interactions in the youth's environment. We consider EP to be more comprehensively focused than TI given the attention paid to both family-level environmental scaffolding and youth-level systems, whereas TI is youth-focused only. The primary change mechanism in both programs is positive decision-making.

We plan to examine both ES factors and traditional RS variables as potential moderators of intervention efficacy. The panel of RS variables includes indices of socioeconomic status, preintervention measures of drug use cognitions, and level of drug involvement. Also included is a *delay discounting task*, a measure of impulsive decision-making and predictor of substance abuse, which has been shown to moderate substance use interventions [61]. Our ES factors include dopaminergic gene variants (combined as a genetic sensitivity score), the Highly Sensitive Child Questionnaire [49], and the post-auricular reflex (PAR, a novel physiological marker of ES). The ES and RS indicators will be composited to form one ES and one RS scale. We aim to investigate the independent and value-added features of ES moderation above and beyond that of traditional RS moderation. That is, does knowledge regarding youth sensitivity levels contribute to appreciable explained variance in outcome heterogeneity above and beyond indices of risk factors and severity of drug use?

CONCLUSION

ES theories attempt to account for variability in developmental pathways given particular environmental exposures. Of interest to prevention scientists are factors that moderate positive environments derived specifically from the ES frameworks of DST, VS, BSC, and SPS. ES moderator variables, which predict differential outcomes to positive environments, such as

those embodied within preventive interventions, may not only explain systematic heterogeneity in preventive interventions but may one day serve as tailoring tools. Given that individuals with lower levels of ES are less responsive to positive environments, they may need more dosage or comprehensiveness in their preventative to achieve optimal responses. Measuring ES as a phenotype before a given preventative may directly aid clinicians in deciding what prevention type or dose youth should receive to optimize outcomes while saving untold costs and reducing burden. However, it is unlikely that such an approach will be successful without the use of other highly predictive tailoring tools and strategies such as Sequential, Multiple Assignment, Randomized Trials (SMART) [62]. Furthermore, ES theories are still in their infancy and there is much debate about their reliability. This moderation framework is focused on quantitative (high versus low ES) rather than qualitative differences in ES. Little is known regarding how uniform ES is as a phenotype; it may very well be that person-centered approaches of profiling multiform ES will be more fruitful in aiding personalized prevention efforts. We encourage others to explore that very idea. It is crucial that, for any putative tailoring tool, strict clinical reliability and validity be ascertained before any practical use. However, we believe that, based on the extant literature, this cause is worth the rigorous investigations, and we encourage research teams to incorporate ES factors into their prevention science.

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Compliance with ethical standards

Conflict of interest: None declared.

Adherence to ethical principals: All authors of this submitted manuscript agreed to comply with all ethical principals as set forth by Translational Behavioral Medicine including the following:

- Full disclosure of conflict of interest, which there is none.
- No data was collected from humans or animals as part of this manuscript; thus, we did not need to obtain informed consent.

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