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Personalizing and Optimizing Preventive Intervention Models via a Translational Neuroscience Framework

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Abstract A new generation of research, building upon developmental psychopathology (Luthar et al. 1997; Luthar et al. (*Child Development*, *71*, 543–562, 2000)), provides evidence that individual differences in risk for behavioral health problems result from intrapersonal and environmental modulation of neurophysiologic and genetic substrates. This transdisciplinary model suggests that, in any given individual, the number of genetic variants implicated in high-risk behavior and the way in which they are assorted and ultimately suppressed or activated in the brain by experiential and contextual factors help to explain behavioral orientations. Implications are that behavioral health problems can be amplified or reduced based on characteristics of an individual and socio-contextual influences on those characteristics. This emerging research has extraordinary implications for the design of prevention programs that more precisely target the malleable mechanisms that underlie behavioral health problems and, hence, more effectively prevent behavioral problems and promote resilience. A detailed, theory-driven examination of all evidence-based interventions is called for to identify the active ingredients that specifically impact these underlying mechanisms. Such an approach will enhance the ability of preventive interventions to achieve effect sizes indicative of beneficial impacts for a greater number of recipients. This paper presents the significant implications of this collective knowledge base for the next generation of precision-based, prevention-focused personalized interventions.

Keywords Transdisciplinary · Translational · Personalized · Prevention · Intervention · Neuroscience

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Introduction

Given the challenge of optimizing program effects to prevent eventual behavioral health problems, it is essential to elucidate individual differences in intervention response via a transdisciplinary research approach. To date, even the most efficacious preventive interventions do not benefit a large number of recipients, as intended (Corrieri et al. 2014); effect sizes may be significant, however they are not indicative of the extent or nature of variability in response. One major reason is that a "one-size-fits-most" model does not account for the complex combinations and multitude of risk determinants.

An integration of developmental neuroscience findings regarding the etiological underpinnings of risk behaviors into social learning theory and prevention science holds great potential to more precisely delineate the sources of heterogeneity in intervention outcomes. To date, subtyping on the basis of observable behavior, surveys, and background characteristics has failed to substantially improve effect sizes. A growing body of evidence points to the possibility that children at risk for behavioral health problems may have distinctive neural signatures that portend differential responses. Such findings are particularly noteworthy when considering that children often targeted by preventive interventions are at risk by virtue of exposure to high levels of adversity (e.g., poverty, maltreatment, trauma), which have been repeatedly associated with altered trajectories of brain development, particularly affecting neural network architecture that undergirds emotion and

behavioral self-regulatory skills. Guided by this knowledge, further refinement of proven prevention strategies and development of new, novel approaches takes into account the role of a major driver of behavior—the brain—to target malleable mechanisms that underlie behavior change. The significance of this approach is reflected in the massive National Institute of Health (NIH) undertaking in the Adolescent Brain Cognitive Development (ABCD) study.

There is a call for a detailed, theory-driven examination of all evidence-based interventions (Gottfredson et al. 2015). This approach requires further investigation into the interplay between social contextual factors and neurodevelopmental features that may moderate a favorable intervention response (e.g., inhibiting inappropriate behavioral responses, being facile in recognizing and regulating emotions during conflictual social interactions, engaging in positive social behavior). If informative, these moderators may function as tailoring variables useful in matching individuals to various types and dosages of an intervention. These developmental prerequisites may further mediate outcomes, providing program developers with critical information to optimize program design for more targeted and efficient delivery. As these fundamental gaps are filled, interventions can be increasingly tailored to more effectively promote adaptive behaviors and reduce risk for behavioral issues.

To address this call, integrative scientific thinkers are trending toward a precision-based paradigm that seeks to target individual "signatures," reflective in interactive biological and social mechanisms, to achieve improved program effects. This strategy was adopted in the field of prevention science from the "precision medicine" model promoted by the NIH as an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. The ultimate goal is to provide tools for practitioners to more accurately predict which intervention strategy will work best and for which subtypes. Principles of precision medicine can be applied in both prevention and treatment across all healthcare disciplines. In the present context, we use the term precision-based prevention to emphasize the specific application of principles of precision medicine in the prevention field.

Newly developed lines of inquiry serve as transdisciplinary models for the application of this approach to prevention from previously siloed fields across the disciplinary spectrum (e.g., neuroscience, endocrinology, genetics, behavioral science, epidemiology). A new language and conceptual framework is emerging that truly integrates concepts of risk determinants, mechanisms, and processes for a more holistic understanding of human behavior. As such, precision-based prevention promises to inform intervention efforts to impact individual recipients and ultimately public health more broadly. Based on studies that have revealed high levels of brain plasticity throughout childhood and adolescence (Eiland and Romeo 2013; McEwen and Morrison 2013; Spear 2013), there is

reason to forecast that preventive interventions precisely targeted to developmental windows of opportunity have potential to optimize or redirect developmental trajectories. This approach serves as a roadmap for research exploring mechanisms of intervention effects.

Translational Framework

A six-phase translational framework (Fig. 1) has been developed specifically for prevention science to guide the construction of precision-based interventions, conduct comparative effectiveness trials, and "institutionalize" resultant programs and practices to achieve broad population level effects (Fishbein et al. 2016). Type 0 translation (T0) refers to how discoveries in genomics, epigenetics, molecular biology, neurophysiology, and the behavioral and social sciences may shed light on etiological heterogeneity and reveal malleable mechanisms in the emergence of at-risk subgroups. Type 1 translation (T1) applies this mechanistic information as a blueprint for developing both screening tools and adaptive intervention strategies. Informed by strategies from engineering, optimizing interventions rely on the ability to identify components that more potently and efficiently move the needle on these mechanisms to alter the outcome of interest; thus, greater precision is achieved. Type 2 (T2) allows for the validation and refinement of the various adaptive intervention strategies via creative designs such as SMART. Type 3 (T3) refers to comparative effectiveness (confirmatory) trials where personalized intervention models are pitted against "one-size-fits-all" models in real-world settings. Type 4 (T4) recognizes that while precision-based prevention can aim to change
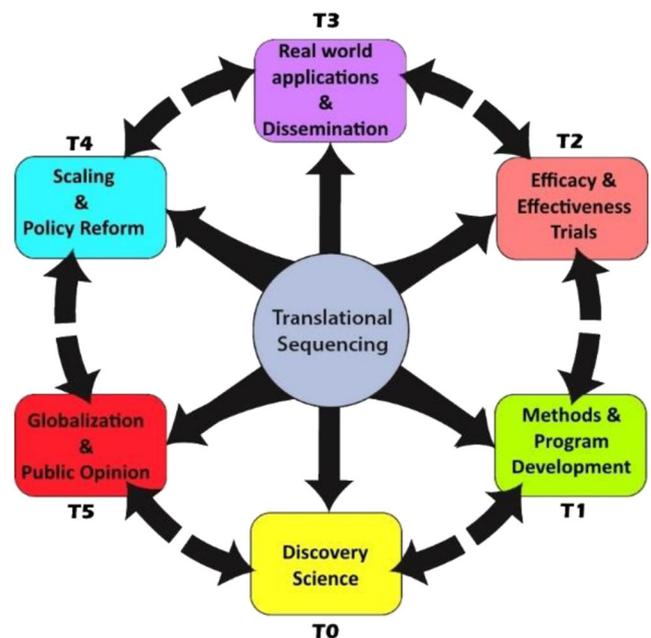

Fig. 1 Translational sequencing

individual behavior, it can also target entire communities by modifying service delivery systems (e.g., systems change, interagency collaboration, genetic counseling), environmental changes through social networks, or instituting targeted policies that are different from one community to the next. And Type 5 (T5), globalizing the application of this knowledge and change in public opinion, has yet to be realized for prevention science. There is a need to reform universal social systems to become more responsive to individual human needs based on sound and well-tested scientific evidence, taking into account global political, economic, and cultural variations. It should be noted that optimal advances within each phase would be informed by evidence from the other five phases. Ultimately, the goal of each [interactive] translational phase, as applied to a personalized prevention approach, is to compel a more effective and compassionate response to behavioral health problems; clinical and public health policies will be increasingly responsive and effective, thereby exerting greater reductions in such problems.

Translational phases 0 through 2 have particular relevance to the present paper. We begin with an elucidation of neurobiological processes and social contextual factors that influence their development shown by T0 discovery science to underlie the behavioral problems we aim to prevent. Given that the functional integrity of these processes plays such an instrumental role in determining behavioral outcomes, carefully constructed interventions designed to improve their functionality are likely to yield the greatest benefits in a precision-based preventive approach. Thus, the next section on T1 discusses the translation of this knowledge to the development of new—or refinement of existing—interventions that are precisely targeted to putative underlying generators of behavioral problems. And third, the section on T2 presents research design options with potential to identify program components that move these mechanistic needles and, in turn, inform optimization of interventions.

Etiological Underpinnings of Behavioral Problems Relevant to Intervention Responsivity

Numerous studies show that interactions between certain genetic susceptibilities, neurobiological integrity, and deleterious environmental conditions have the potential to produce a sequence of behavioral phenotypes throughout development that bias the trajectory toward poor behavioral health outcomes (Bronfenbrenner and Morris 2006; Shonkoff 2010). One significant pathway to behavioral problems is theorized to emanate from a deviation in neurological development, expressed as deficits or delays in neurocognitive and emotional regulatory functioning. Dysfunction in executive cognitive functioning (ECF) has been a significant focus of this research given feedback loops between the neural substrates of ECF

with emotional centers of the limbic system. ECF has multidimensional attributes primarily modulated by the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) and that are supported by several secondary cognitive, emotional, and motor systems (i.e., elementary cognitive processes such as sensation, perception, and motor activation that recruit diverse neural systems throughout the brain). ECF comprises domain-general cognitive processes that are active in response to novel or abstract problem types for which no prior problem-solving method or knowledge base exists. As found in various cognitive psychological studies from information processing (Miyake et al. 2000) to neuropsychological and neurobiological perspectives (Norman and Shallice 1986; Posner and Rothbart 2000; Welsh et al. 1991), these cognitive functions include those involved in holding information in working memory, inhibition of prepotent or extraneous information, and appropriate goal-directed sustaining and switching of attention. Generally speaking, ECF refers to effortful cognitive processes, as opposed to relatively automatic aspects of cognition associated with crystallized knowledge and semantic and declarative memory processes.

Executive skills do not act alone in generating behavior; they interact with neural and psychophysiological substrates of emotional tone, arousal, and reactivity in response to environmental contexts (Bell and Wolfe 2004; Blair 2002). These cognitive and affective processes appear to be reciprocal in that effortful cognitive inhibition may be a prerequisite for the ability to self-regulate emotional responses and, at the same time, regulation of affective responses supports the ability to generate effective strategic planning and coping behaviors (Eisenberg et al. 1998). As a result, dysregulated behavior may be fueled by individual differences in the cognitive control and affective processing systems that underlie goal-oriented behavior. Dysfunction in neurobiological systems subserving ECF and emotion regulation leads to increased sensation and novelty seeking (Joireman et al. 2003), insensitivity to aversive conditioning (Fowles 2000), and very low tolerance of frustration (McKay and Halperin 2001) that often accompanies dysregulated behaviors. Given the developmental nature of this cortico-limbic circuitry, manifestations of dysfunction in this circuitry vary as a function of maturational stage. e.g., young children may exhibit poor academic achievement, aggressiveness, conduct problems, negative affect, impulsivity, and other constructs. Over time, these behaviors increase risk for early behavioral problems and psychopathology by young adulthood.

Of great importance to prevention science, social contextual factors confer significant influence on these emergent cognitive and emotional regulatory functions. Brain development and, in turn, brain functioning are exquisitely sensitive to environmental inputs, thereby increasing risk for, or protecting against, dysregulatory outcomes, contingent upon the nature of those experiences or exposures (Shonkoff and Garner 2012). Severe

psychosocial stress is particularly impactful because it has been shown to alter development and function of the PFC and limbic system, potentially contributing to ECF and emotional delays or deficits (Koenen et al. 2001). Thus, children who are emotionally reactive and poorly regulated, and are also developing in environments that cannot optimize and support their regulatory deficits, will likely be at risk for atypical neurocognitive and socioemotional trajectories. However, these same children raised in environments with adults who support language development and regulatory skills (e.g., emergent executive functions) may be less apt to exhibit dysregulated behaviors. Determining the role of stress in the ability to respond favorably to intervention can guide development of strategies that more precisely target its functional consequences.

Informing Intervention Development via Developmental Neuroscience

The translation of neuroscience findings that pertain to the emergence of behavioral health problems to intervention models is now recognized as an important pathway for prevention science. Critically, the neurocognitive and emotional processes elucidated above are malleable and have been shown to respond favorably to appropriate interventions (Brody et al. 2017; Jimura et al. 2010; Piehler et al. 2014; Riggs et al. 2006). Given that relative deficits in ECFs may place children at risk for developing behavior problems, it may benefit children who demonstrate weak or delayed cognitive skills to intervene early, intensively focusing on strengthening otherwise weak cognitive connections. By doing so, researchers can either apply a new component to—or a more intensive version of—intervention with the goal to enhance children's cognitive skills in the service of reducing future behavior problems. Children with poor executive skills may also benefit from environments that promote ECF development. A highly relevant study found that early educational enrichment programming produces long-term enhancements in physiological markers of arousal and stress in 3- to 5-year-olds (Raine et al. 2001). Also, Fisher found cortisol dysregulation to be malleable in response to an early childhood intervention targeted to specific needs of foster care children (Fisher et al. 2000). Several additional studies also provide evidence for the impact of a targeted intervention on cortisol responsivity (Laurent et al. 2014; Gaab et al. 2003, 2006; Hammerfald et al. 2006; Mommersteeg et al. 2006) suggesting the potential for stress reduction to mediate outcomes. Overall, clinical studies of head injury, learning disability, and cognitive disorders suggest that both underlying neurobiological processes, from HPA responses to ECF, and related behaviors are amenable to precision-based interventions that specifically target underlying mechanisms (Bierman et al. 2008; Brody et al. 2017; Davidson et al. 2003).

The premise is that intervention effects (or the lack thereof) will be observable at transitional times of greater demand for self-regulation as a function of level of neurocognitive abilities. During transitional periods in development, when mental resources are challenged, existing deficits become manifest, if not exacerbated, in an effort to deploy necessary cognitive skills for coping. Precursors for developmental delays in ECF, as well as dysregulated behavior, emerge and become more visible during the early school years when children undergo a major developmental transformation that involves increases in cognitive skills and changes in brain size and function (Anderson 2002). This transition and accompanying developmental change allow children to significantly advance in responsibilities, independence, and social roles (Belsky and MacKinnon 1994). Thus, relationships between affective understanding, cognition, and behavior are of crucial importance in socially competent action and healthy peer relations that manifest during this early childhood period (Elias and Weissberg 2000).

Precision-Based Research Designs

Several research designs are presented in this section that enable optimization of interventions to more precisely move the mechanistic needle. As stated, small to modest effect sizes characterize most preventive interventions, particularly those that are universal (Evans and Weist 2004; Greenberg et al. 1995; Weisz et al. 2005). Similar effect sizes are common in medicine (effect of aspirin on heart disease is actually lower) and in education (findings on class size and achievement) (Cooper et al. 2009). However, such moderate effects have a large population impact on outcomes (Bloom 2006; Offord 2000) and many argue that the percentage of reduction in risk is a more useful metric for prevention trials. In a universal model, one would not expect to substantially change most of the population as they are not all high risk, e.g., children who already show positive social emotional development are not likely to substantially improve. It is also possible that children with particular needs not being met by the current design of any given intervention would not respond as well as others who are more appropriately suited to the intervention. Thus, identifying who is most vulnerable versus who is improving is an approach more likely to reveal where the more substantial impact of the intervention actually occurs in the population. This process requires examining and utilizing individual differences to inform program selection and adaptations. Targeted enhancements can then be designed within a school-, community-, or family-based program that offers both a general benefit and components that target those most in need.

The research design chosen is critical in the ability to identify "who" is responding best to an intervention and "why." The gold standard is the randomized controlled trial (RCT)

because it is most likely to produce unbiased and consistent efficacy relative to other designs. And RCTs are, in fact, considered prerequisite to establish a program as "evidence-based." Traditional RCTs do not, however, necessarily address the heterogeneity among recipients that contribute to differential responsivity; rather, results are reflective of "central tendencies" that are not applicable to individual participants (Kazdin 2010; Shadish et al. 2008; Williams 2010). And many studies that stratify often do so on the basis of characteristics (e.g., gender, sex, ethnicity, psychological traits, parental attributes) that are not mutable processes. This practice is limiting in its focus largely on program effectiveness by testing aggregate behavioral outcomes in a population and not accounting for differential effects between children stratified by functional markers of responsivity. As a result, interventions are not yet sufficiently informed by research that more precisely identifies mechanisms underlying high-risk status or differential responsivity. Designs that elucidate mechanisms of behavioral change, based on individual level characteristics and components of interventions that are essentially active ingredients for those individuals, are best suited to address precision-based questions.

Once these mechanisms are identified and sufficiently studied, additional investigation will be needed to understand what, if any, program adaptations are needed and for whom (e.g., participants with varying responsivity) to ensure program success. This strategy calls for effectiveness-implementation hybrid designs (Curran et al. 2012). These designs are different from those that examine which program components work best for participants by additionally assessing implementation factors that may impact participant responsivity (e.g., clinician and/or setting characteristics among other factors). Thus, there are implications for how to best train program implementers to identify participant needs and incorporate adaptations to meet those needs. This approach differs from a traditional emphasis on fidelity of implementation and calls for a greater utilization of implementation science principles and framework (Meyers et al. 2012) and process evaluation data when designing and studying program effectiveness. While fidelity of implementation is important, real world contexts, constraints, and ecological validity require that interventions positively affect heterogeneous groups of individuals. Personalization of program components based on that heterogeneity has potential to improve outcomes. Mapping these components to participant responsivity and adaptations to create decision rules for implementers and service providers will more precisely address heterogeneous needs of samples and subgroups.

Moderation and Mediation Designs

The process of personalizing and optimizing prevention programs relies heavily on the identification of individual characteristics that predict differential outcomes which, in turn, may shed light on the intervention's targets for change. Determining whether baseline differences and/or variability in aspects of individual development influence intervention response guides the targeting of program types to potentially responsive subgroups. As such, moderators serve as tailoring variables with potential to enhance precision by matching individuals to their most effective interventions. Furthermore, identifying these predictors can inform program refinements to be better suited for characteristics that portend favorable versus unfavorable outcomes. One technique referred to as "microtrials" involves randomized experiments that use brief psychosocial manipulations designed to identify conditions or characteristics that moderate pre- to post-intervention effects but are not expected to lead to long-term change (Fishbein et al. 2006; Howe et al. 2010). These experiments are relatively inexpensive and provide solid ground for the design of more targeted interventions as well as subsequent full scale RCTs.

Mediation models, including measures of malleable processes that underlie behavioral problems, are also needed to determine whether change in functional markers from pre- to post-intervention leads to improved behavioral outcomes over time. To elucidate *how interventions work* by evaluating individual differences in outcomes, and how individuals change (not to evaluate program effects), a theoretical model drawn from etiological research is suggested (MacKinnon 2008).

An understanding of variability in intervention efficacy can be discerned via the use of a multiple-levels approach (Cicchetti and Blender 2006; Fishbein 2000; Fishbein et al. 2006; Greenberg 2006; Luther and Cicchetti 2000). Cognitive and emotional processes are potentially malleable and may respond favorably to appropriately designed interventions, thus mediating their effects (Hermann and Parente 1996; Manchester et al. 1997; Riggs et al. 2006; Rothwell et al. 1999; Wilson 1997). Ultimately, knowledge generated from this approach will highlight areas in need of improvement for classes of preventive interventions that are used in many settings and the design of new components that are better suited to various subgroups. Use of a multiple-levels approach—akin to the bio-ecological framework of multiple systems simultaneously impacting behavior (Bronfenbrenner and Morris 2006)—offers optimism that preventive intervention research will continue to advance in terms of its sophistication and comprehensiveness and translational efforts to develop interventions that promote resilient functioning will be fostered.

Multi-Phase Optimization Strategy

Multi-Phase Optimization Strategy (MOST) (Collins et al. 2011, 2014a, b, c, 2016) is an innovative methodological framework for building more efficient, effective, and scalable

behavioral interventions. Inspired by engineering principles, MOST is a three-phased approach that includes preparation, optimization, and evaluation. Preparation involves a review of the empirical literature, development of a conceptual model of the mechanisms, identifying intervention strategies that target certain parts of the conceptual model, and conducting pilot studies to assess feasibility and acceptability of intervention components targeting the underlying mechanisms. Optimization is defined as the process of finding the best possible solution, subject to given constraints. Highly efficient experimentation permits the empirical examination of the effectiveness of each component on each hypothesized mediator and outcome, then selecting the most effective set of components to comprise an optimized intervention to be evaluated with an RCT. The uniqueness of MOST in prevention science is the requirement that mechanisms be identified and optimization performed *prior* to evaluating efficacy; the majority of prevention studies do not test for mechanisms or allow that process to guide the optimization process. This approach enables creation of a highly effective and efficient intervention that specifically targets mechanisms of change, which essentially facilitates scalability.

Sequential Multiple Assignment Randomized Trial

Sequential Multiple Assignment Randomized Trial (SMART) is an empirical approach, also with roots in engineering, to adapt interventions to participants' responsiveness (Murphy 2005; Rivera et al. 2007). This approach requires timely data availability and analysis to inform decisions as to whether a participant should continue the current intervention or program component (if they are positively responding) or be assigned to another component when they are not responding well, i.e., mechanistic needles are not moving or outcomes are not favorable. Data-driven decisions are based on participant outcomes to the current intervention component. This allows for rapid responses to participant performance. Although SMARTs have been used for large-scale intervention studies, the findings and approach can be applied to both smaller samples and patient populations. This approach reveals for whom a certain sequence of program components is most potent, with one component being effective for some responders and a different sequence demonstrating greater effectiveness for others. From these trials, an algorithm can be devised with decision rules for intervention providers.

Other Adaptive Approaches

The implications of approaches used in precision medicine for personalized prevention through adaptive Evidence-Based Practices (EBPs) are substantial. As noted above, adapting programs to target mechanistic characteristics that compromise program responding, while maintaining the core program components, has great potential to positively improve participant outcomes and result in greater effect sizes. Some programs are more adaptive than others, meaning they are amenable to being continuously revised based on individual or subgroup level responses. Participants found to possess mechanistic characteristics that interfere with a program's potential benefits warrant modifications to protocols or strategies. Client or person-centered programs are even more amenable to these adaptations given enhanced flexibility when working with single cases. For example, Motivational Interviewing (MI) and Screening, Brief Intervention and Referral to Treatment (SBIRT) are two approaches that, by their very nature, lend themselves to timely information to adapt to individual characteristics. MI is a semi-directive, client-centered counseling style for behavior change that examines and resolves ambivalence about certain behaviors to facilitate and engage intrinsic motivation within the client for sustained change (Miller and Rollnick 2002). SBIRT utilizes universal screening to identify more tailored, short, personalized early treatment programs. These programs are most notably used to address alcohol and other substance use needs (Barbor et al. 2007). Short-term behavioral improvements have been widely demonstrated; however, mechanisms of effects have not yet been delineated and long-term behavioral change needs further investigation. With information from precision-based approaches, MI, SBIRT, and other adaptive approaches can be refined to achieve greater effects (Madson et al. 2016).

Example of an Intervention Strategy Amenable to Greater Precision

Mindfulness-based programs—such as mindful yoga—have been shown to positively impact coping and stress management via strengthening emotional regulation and cognitive control among people of all ages (Dariotis et al. 2016a, b, 2017; Davidson et al. 2003; Gould et al. 2012; Mendelson et al. 2010, 2013). Implementation of school-based mindful yoga programs in inner-city public schools has been amenable to identifying the plausibly causal role of various forms of adversity (e.g., poverty, maltreatment, and stress) on desired program outcomes, such as inhibition, self-regulation, planful competence, awareness, and reduced symptoms of affective disorders. There are several components inherent to most mindful interventions that likely have differential impacts on these various outcomes, such as breath work, meditation, postures, and relaxation exercises. As such, mindful yoga is particularly amenable to a precision-based approach given well-defined core program components as well as the wealth of knowledge being amassed on underlying mechanisms of effects (Gould et al. 2016). There is growing empirical support for improvements from mindful yoga participation in well-being, overall health, and prosocial behavior by affecting homeostatic systems that modulate neurophysiological

responses to stress as well as executive controls such as attention and awareness of bodily sensations and emotions and sleep patterns in the service of emotion regulation (Froeliger et al. 2012; Garland et al. 2013; Rocha et al. 2012). Indeed, neuroimaging studies in other populations and age groups have established that mindful yoga improves brain function in measurable ways, demonstrating the alterability of these underlying mechanisms (Davidson et al. 2003).

Program components can be readily disaggregated and subjected to factorial experiments or comparative trials to determine which are most active in altering these mechanistic processes. Figure 2 exhibits a logic model whereby breath work, postures, meditation, and focused attention are the primary components of mindful yoga. These activities have been empirically shown to alter neurophysiological processes associated with executive cognitive control over affective responses, quality of sleep, and reactivity to stressful stimuli (Davidson et al. 2003; Gard et al. 2014; Pagnoni et al. 2008; Rocha et al. 2012). Delineating the specific ingredients of the program that act on these malleable mechanisms is the next step to personalize the program to benefit a greater number of participants who present with heterogeneous traits, experiences and physiologies that interact with program components to portend differential outcomes.

Personalizing and Optimizing Prevention

The objective of a precision-based approach to preventing behavioral health problems is to guide protocol refinements that improve potency and, at the same time, remain sensitive to the needs and challenges faced by the target population, thus promoting a high level of engagement, feasibility, and acceptability. Using precision-based designs to engineer a more personalized and optimized intervention will enable targeting of underlying mechanisms for improvement of specifically mapped outcomes. The potential payoffs are rooted in several areas. First, this approach makes efficient use of research resources and improves the scientific yield by using

efficient experimental designs, many commonly used in engineering but less familiar in prevention science. Precision-based interventions are more economical, utilizing fewer resources and optimizing on malleable mechanisms with greater benefits to those most in need. The alternatives are more costly in terms of eventual mental health problems, incarceration, and other negative outcomes that far exceed the cost of intervention (Noser et al. 2017). Also, results afford greater specificity in informing future research on differential responsivity.

Second, resultant interventions become more transparent in that it is clear which components are more or less effective for which individuals or subgroups based on well-defined characteristics that hamper or promote favorable outcomes, leading ultimately to further revision of both individualized and universal interventions. Also, there are opportunities to only bring forward the active ingredients, thereby enhancing effective scalability. This personalization process provides a starting point for subsequent research to systematically and incrementally progress toward even more effective, efficient, and appropriately targeted interventions.

Third, data generated contributes to secondary analyses investigating the effectiveness of *each component* within subgroups of individuals. And fourth, an in-depth formative process is recommended to augment the findings previously generated by efficacy and effectiveness trials with the intervention to ensure that the curriculum is culturally and developmentally appropriate for the target population, as well as meets any special needs (e.g., trauma history, mental health concerns, learning disability). The results will provide valuable information for the development of highly tailored, adaptive interventions (Collins et al. 2014b).

Although these approaches are in their infancy and may be perceived by some as more ideological than practical, the field generally is moving in the direction of personalizing and optimizing prevention (in addition to scaling existing interventions for a population level impact) to achieve larger effects sizes. Selective and targeted models, such as the work of Conrod that focuses on personality determinants of intervention effects (e.g., O'Leary-Barrett et al. 2016), are strong and
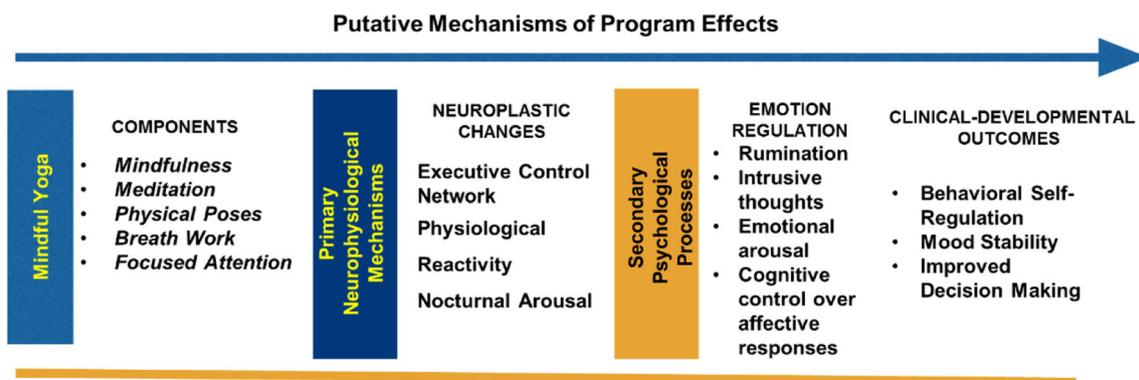
Fig. 2 Putative mechanisms of program effects

rigorous but they do not address individual differences within determinant category (e.g., externalizing or stress reactivity) which may be related to variation in responsivity. Rather, what is needed is an innovative approach that may be high-risk (e.g., cost of studies and programming) but high-reward (e.g., positive outcomes and reduced social and human costs). Starting with what we know, developing algorithms for those programs, and further refining them as we accumulate more data is how we can improve effectiveness. Given that this work is so innovative, in formative and exploratory stages, sample size recommendations are not practical. And in terms of affordability, the cost of these designs must be empirically derived with adjustments for the return on investment (ROI), which will inform the balance between precision and cost.

Conclusions

There is a critical need for science-based prevention programming to optimize individual potentialities in the context of prevailing social and biological conditions. The ability to effectively utilize existing external resources, make adaptive choices, and reach potentialities depends on ECF, emotion regulation, and their neural and social supports. In the absence of favorable external resources and developmentally appropriate brain function, behavioral health problems are more likely develop. Delineating the underlying neurobiological mechanisms and the ways in which social contextual experiences and exposures is, therefore, essential. To effectively strengthen these conditions, prevention programs will be infinitely more effective when they more precisely address malleable neurobiological and social aspects of self-regulation. Future studies to shed light on these interrelationships can contribute to the refinement or design of targeted interventions that impact critical points in the developmental trajectory to alter risk status. The ultimate goal is that, through a transfer of knowledge from etiology to practice and back to etiology, clinical and public health policies will be increasingly responsive, applicable, and *precision-based*, thereby exerting greater impacts.

Specific recommendations for facilitating this line of work are delineated below:

1. Training grants geared toward preparing young scholars to not only conduct the research but to incentivize a focus on translation to practice
2. Transdisciplinary academic (dual-title) programs that provide the cross-cutting knowledge and experience for early career investigators
3. Braided funding (e.g., NIH and SAMSHA or CDC), closely tied to academic degree programs, that focuses on research, training, and practical applications

4. Commissioning textbooks and/or handbooks with the instructional content to promote a precision-based approach
5. Engage foundations (e.g., Robert Wood Johnson, William T. Grant, etc.) in the process given their inherent interest in bringing life to research
6. Encourage relevant societies (e.g., Society for Prevention Research, Society for Research on Child Development) to provide a thematic focus on precision-based prevention and provide fellowships to early career investigators
7. Educate practitioners and organizational and agency heads regarding the implications of this research to aid in the development of supportive infrastructures
8. Employing implementation science strategies and principles to examine implementation-related factors that impact individual differences in intervention reactivity

In summary, as the field moves toward precision prevention, the next generation of transdisciplinary scholars and service providers requires training in implementation science, adaptive and hybrid design methodologies, and real-time data-informed decision-making about program adaptations. Personalized programming requires openness to adaption and ability to modify treatment on an ongoing basis not customary in one-size-fits-most programs. Greater human capital, such as training, staffing, and organizational capacity building, is needed to continuously evaluate and re-evaluate how participants respond to programs. This requires vigilance to changing data patterns (outcomes) and ability to interpret data to make treatment decisions (e.g., decision trees and/or algorithms) to translate into programmatic changes.

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