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Microtrial Methods for Translating Gene-environment Dynamics into Preventive Interventions

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Abstract

Genetically informed research on behavioral outcomes holds substantial promise for guiding efforts to enhance the efficacy and effectiveness of preventive interventions, but it also poses considerable challenges given the complexities of the dynamic interplay between genes and environment. This paper introduces a relatively uncommon research design, called microtrials, to provide a means of translating basic research findings into prevention trials, particularly through introducing genetic effects into prevention models. Microtrials are defined as randomized experiments testing the effects of relatively brief and focused environmental manipulations designed to suppress specific risk mechanisms or enhance specific protective mechanisms, but not to bring about full treatment or prevention effects in distal outcomes. Microtrial methods are described in detail, with discussion of their unique advantages for translating this knowledge base into prevention research. We end by raising several issues to consider when constructing genetically sensitive microtrials.

Keywords

Efficacy trials; Gene-environment interaction; Microtrial; Research design; Translation

Understanding the interplay of genes and the environment is a necessary first step for any effort to use the environment to reprogram and reduce genetic risk. However, it is clear that this interplay is complex, dynamic, and can be difficult to replicate (Risch et al. 2009). Nonetheless, the substantial benefits for prevention efforts of understanding this interplay are suggested by both animal and human research. For example, Suomi (2009) demonstrated that if monkeys at genetic risk are raised in a more supportive social environment, excessive alcohol consumption disappears. This effect has parallels in studies conducted with human subjects: parental monitoring of their children's whereabouts and activities substantially alters the impact of genetic loading on adolescent smoking (Dick et al. 2007). These findings reflect *gene-environment interaction (GxE)*, in which variation in gene polymorphisms moderates the impact of environmental factors on the development or onset of a disorder. There is now

evidence for gene-environment interactions in the etiology of such conditions as major depressive disorder (Uher and McGuffin 2008), post-traumatic stress disorder (Binder et al. 2008), and externalizing behavior (Kim-Cohen et al. 2006), although debate continues about the presence of particular GxE effects (Risch et al. 2009), and the physical basis of such effects (Beach et al. 2010; Liu et al. 1997; McGowan et al. 2009). The interplay between genes and environment is likely to extend beyond simple interaction effects, and we prefer the term *gene-environment dynamics* to capture the complexities of this emerging field.

Genetically informed research on behavioral outcomes holds substantial promise for guiding efforts to enhance the efficacy and effectiveness of preventive interventions, but it also poses considerable challenges given its potential complexity. For example, investigators have begun to study how genetic variation might moderate the effects of existing preventive interventions. In a randomized trial of a family intervention designed to delay initiation of risk behavior in rural African American youth during early adolescence, Brody et al. (2009b) collected and genotyped youth DNA for variation in the serotonin transporter (5-HTTLPR) gene. The intervention was protective for children with a specific allele of that gene, with evidence suggesting that this protection was conferred by high levels of involved-supportive parenting that decreased youths' opportunities to engage in risk behavior (Brody et al. 2009a). Bakermans-Kranenburg and her colleagues (2008) conducted a randomized trial of a parent-training program designed to increase rates of sensitive discipline in parents of 1- to 3-year-old children; they also collected and genotyped child DNA for variation in the dopamine D4 (DRD4) receptor gene. The intervention reduced subsequent externalizing behavior only in the children having a particular form of the DRD4 gene, and the greatest effects involved those children with that form of the gene in the intervention group who were also exposed to the highest levels of sensitive parental discipline.

Both of these studies found that children with a particular genetic signature gained protection from participating in preventive interventions. Because they utilized experimental designs, these studies provide evidence of GxE effects that complement and extend data from non-experimental designs. In addition, the experimental designs of these studies can greatly increase their power to detect interaction effects as compared to correlational field studies (McClelland and Judd 1993). However these studies have only limited capacity to explain why particular children benefit or provide clues as to what risk mechanisms should be targeted in children who do not benefit. Finding the answers to such questions requires studies of the mechanisms through which risk and protective factors exert their effects, and of the ways in which these mechanisms differ based on genetic variation. Although randomized trials of full-scale interventions can provide some insight into these questions (Howe et al. 2002), their utility is constrained by the considerable cost and effort required, and by the complex and multifaceted nature of the interventions employed.

In this paper, we suggest that a relatively uncommon research design, which we call *microtrials*, can provide a key means of translating basic research findings into prevention trials, particularly in the realm of introducing genetic effects into prevention models. It can do so by providing precise and contextually nuanced information about gene-environment dynamics, thereby increasing prevention researchers' ability to translate genetically informed etiologic research into more effective prevention programming. In particular, a microtrial approach can illuminate risk and protective mechanisms that account for observed GxE effects, and so offer guidance in the construction of flexible prevention programs that can respond to these processes.

We first discuss the current status of gene-environment interaction research that provides the foundation for translation. Next, we introduce microtrial methods and discuss their unique

advantages for translating this knowledge base into prevention research. We end by raising several issues to consider when constructing genetically sensitive microtrials.

Studies of Gene-environment Interaction

Research on the serotonin transporter gene as a moderator of environmental effects constitutes perhaps the most extensive body of findings relevant for prevention researchers at this time. The serotonin transporter is a protein that moves the neurotransmitter serotonin from the synaptic cleft back to the presynaptic neuron. The human serotonin transporter gene (SLC6A4) is involved in the production of this protein. This gene has a promoter region (5-HTTLPR) that controls transcription, and different polymorphisms within this promoter region have been found that lead to different rates of transcription (Bradley et al. 2005; Lesch et al. 1996; Philibert et al. 2007). These involve short and long alleles, with the short allele associated with lower transcription efficiency and, therefore, less reuptake of serotonin (Philibert et al. 2008). There is considerable convergence across multiple lines of evidence suggesting that the serotonin transporter plays an important role in multiple outcomes of interest to prevention researchers, including migraine headaches, major depression, autism and alcoholism (Conroy et al. 2004; Feinn et al. 2005; Glover et al. 1993).

Research with humans on the interaction of 5-HTTLPR with environmental conditions incorporates three distinct paradigms. Laboratory experiments have been used to determine whether individuals with different polymorphisms respond in different ways to different sets of environmental stimuli. Several f-MRI studies find that carriers of the short allele demonstrate increased amygdala activation to angry faces or aversive stimuli compared to neutral images, whereas those without this allele do not demonstrate such differential reactions (Hariri et al. 2002, 2005). Canli and Lesch (2007), reviewing this research, suggest that 5-HTTLPR may be more broadly implicated in social cognition in ways that shape risk for emotional disorders.

Genetically informed correlational field studies constitute a second paradigm. Most of these studies involve attempts to identify gene-environment combinations that predict the occurrence of depressive disorders or depressive symptoms. Findings from these studies are more complex. Some studies provide evidence that 5-HTTLPR moderates the effects of stress on depression, both when that stress involves early adversity such as child abuse (Caspi et al. 2003) and when it involves recent stressful events (Kendler et al. 2005). In these studies individuals carrying the short allele are at increased risk for depression under conditions of adversity or stress. Other studies have failed to replicate these findings (Surtees et al. 2006), and under some conditions opposite effects are found. A recent meta-analysis concluded that there is no consistent evidence that this GxE pattern is related to onset of major depressive episodes (Risch et al. 2009). However this meta-analysis did not include a substantial group of studies measuring continuous variation in depressive symptoms, which show more consistent GxE effects. In addition, Monroe and Reid (2009) have noted that very few genetically informed studies have used time lags appropriate for the effects of major life stressors, or assessments of stressful events that are sensitive to contextual variation. In addition, as noted, earlier field studies may not be the best means of detecting interaction effects (McClelland and Judd 1993); the experimental laboratory studies described earlier are more sensitive to such effects even with much smaller samples. In addition, studies of simple GxE interaction may not be sufficient to capture the complex mechanisms involved. For example, Kaufman et al. (2006) in their study of maltreated children found a four-way interaction, such that maltreated children with the short 5-HTTLPR allele, the *met* allele of the BDNF genotype, and low current social support from the child's primary support had the highest rates of depressive symptoms. Such findings reinforce the importance of attending to more complex and dynamic patterns of gene-environment interplay, patterns which may be difficult to detect using correlational designs.

Third, as described previously, serotonin transporter genotyping of participants in one randomized prevention trial has been used to study differential effectiveness of preventive interventions (Brody et al. 2009a, b). Youth with the short allele did not enter the program at increased risk. They did not engage in more problem behavior at pretest, and their parents were no less likely to engage in regulative-communicative parenting. Yet evidence indicated that family-based interventions reduced later onset of risk behavior only in these youth. These results are open to two interpretations. The short allele may confer risk that begins during this developmental period, such that youth with the short allele were at increased risk for developing problem behavior, and the parenting intervention suppressed that risk. However, the short allele may actually confer protection through increasing youths' receptivity to positive changes in parenting. These are not mutually exclusive, and are consistent with Boyce and Ellis's (2005) conjecture that 5-HTTLPR may influence emotional sensitivity to both positive and negative environments (see also Belsky et al. 2009).

These findings have three general implications. First, the *mechanisms* that increase or protect against risk for disorder may vary by genotype in complex ways. Distal outcomes such as depressive disorder may sometimes be the result of complex dynamics involving a number of genes interacting with a variety of environmental factors. If this is the case, any single gene or GxE combination will account for relatively small amounts of variance in these outcomes. We suggest there will be greater profit in studying how gene-environment combinations shape specific risk or protective mechanisms than in searching for simple genetic or GxE explanations of distal clinical outcomes.

Second, the *malleability* of a particular risk or protective mechanism may vary by genotype. Preventive interventions may have to be flexible in targeting risk or protective mechanisms in order to be maximally effective for a wide range of participants. Third, it is possible that the effectiveness of specific change mechanisms in a preventive intervention may vary by genotype. In this case, different preventive intervention formats may be necessary to maximize effectiveness for different participants.

These broad implications suggest that passive correlational designs and laboratory studies of brief stimulus effects, by themselves, cannot provide rigorous tests of differential malleability or differential change mechanisms. Full-scale randomized prevention trials with genetic assessment can in principle examine differential malleability and test mechanisms of change by including variations in targeted mechanisms and intervention formats. However, full-scale trials will typically be too cumbersome for this approach, and the strategy is also limited by the substantial costs involved in fielding such trials, the large number of participants necessary to test for genetic moderation, and the small number of trials available to support such tests. It follows that new and more efficient designs are necessary to identify the most promising ways of translating findings into effective interventions that capitalize on emerging knowledge about gene-environment dynamics. We suggest that microtrial designs hold great promise for achieving this goal.

Microtrial Designs

We define microtrial designs as randomized experiments testing the effects of relatively brief and focused environmental manipulations designed to suppress specific risk mechanisms or enhance specific protective mechanisms, but not to bring about full treatment or prevention effects in distal outcomes. Microtrials are designed to test the malleability of specific risk or protective factors and to provide information concerning whether and how specific program components bring about meaningful change in those factors. Microtrials can therefore bridge between laboratory or field studies and full-scale trials, providing key tests of whether and under what circumstances a risk or protective factor is a suitable candidate for targeting.

Genetically informed microtrials can also help determine what specific combinations of intervention components and change mechanisms provide maximal impact for which participants, building on basic research on gene-environment dynamics.

Precursor Designs Studies using a design of the kind we are suggesting for the explication of GxE and other genetic effects are rare, although a few investigators have begun employing similar designs to study other questions. For example, in order to test the malleability of social competencies needed to avoid peer pressure, Fishbein et al. (2006) randomly assigned male adolescents to either an experimental or control group. The experimental group participated in a single session, taken from the Positive Adolescent Choices Training Program, a prevention program for high risk adolescents designed to reduce involvement in violence. The session focused on specific ways of defusing confrontations without aggression. Posttest measures of putative protective factors involved assessment of socially competent responses to several vignettes presented by computer in a virtual reality format. The effects of this brief intervention depended on factors measured at pretest: only adolescents who scored higher on measures of executive functioning and emotion perception demonstrated gains in social competence immediately after the workshop. Although this study does not focus on genetic variation in intervention effect, it does contain many of the elements necessary for a genetically informed microtrial, including an experimental design for testing whether an important protective mechanism can be influenced by a specialized intervention component and whether effects vary for different groups of children.

Gottman et al. (2005) provided an example of an experimental study designed to compare the effects of different intervention components on proximal outcomes. They devised what they termed *proximal change experiments* to test the immediate effects of one-time couples' workshop sessions on subsequent patterns of observed couple interaction. They designed several different brief workshops to either improve friendship or regulate destructive conflict. They found that, as expected, different workshop content changed different aspects of couple interaction. This study also contains elements of microtrial design, in this case comparing the effects of different intervention components designed to change different sets of protective mechanisms.

Microtrials and Prevention Science

We suggest that microtrials can fill an important gap in prevention science, particularly as we begin to examine ways to enhance preventive programs by integrating information about gene-environment dynamics. A report commissioned by the Institute of Medicine (Mrazek and Haggerty 1994) advanced the idea that prevention science would benefit from engaging in a preventive intervention research cycle to develop and test empirically grounded programs. In this cycle, research on risk and protective mechanisms provides the foundation for designing prevention programs that directly target these mechanisms in order to reduce risk for future disorder. Models of risk and protective mechanism, particularly those emerging from the field of developmental psychopathology (Coie et al. 1993), are thus key guides for the development of effective prevention programs. Research on gene-environment dynamics increasingly informs our understanding of developmental psychopathology, and as such can provide an expanding knowledge base for these efforts.

However, the leap from basic findings derived from laboratory or correlational studies to prevention trials can be difficult, with few guideposts along the way. We suggest that microtrials can help fill this gap. As illustrated in Fig. 1, the microtrial represents a key translational step linking basic research to preventive intervention efficacy trials (Note that subsequent steps in the research cycle to determine effectiveness, engagement, and dissemination are not presented in the figure).

Because microtrials are more versatile than full-scale prevention trials and focus directly on malleable mechanisms in context, they provide a more nuanced understanding of findings from basic research, indicating whether or not these findings are appropriate for inclusion in preventive trials. If no evidence of malleable mediating mechanisms can be demonstrated in a microtrial, implementation of a full-scale prevention trial based on basic findings is unlikely to be worth the considerable investment it would involve. At the same time, microtrials allow findings from basic research contexts to be examined under contextually realistic conditions, increasing confidence that basic results can be successfully translated into practical interventions. In this way, microtrials help refine the observations drawn from basic research and transform them into processes better suited for use by those developing, modifying, and expanding preventive interventions. In addition, microtrials are an efficient and relatively inexpensive means of determining whether putative mechanisms are in fact malleable, and thus represent a practical tool for early-career prevention scientists who seldom have the resources to mount full-scale trials.

Design Elements of Microtrials

As summarized in Table 1, microtrials borrow and integrate design elements from three different research traditions: randomized laboratory studies, passive correlational field studies, and randomized full-scale prevention trials. Microtrials utilize randomized experimental methods such as those employed to study etiologic processes in the laboratory. These methods include careful specification and application of standardized ways of manipulating the environment, careful measurement of person characteristics, stratified random assignment to experimental conditions, and standardized assessment of outcomes involving behavior, thought, or affect considered to be theoretically relevant for etiology.

Microtrial designs build on laboratory methods but differ from them in fundamental ways. Microtrials involve exposure to longer and more complex environmental conditions, designed in ways that would allow their use as components of a full-scale intervention. Both basic laboratory studies and microtrials employ conditions tailored to alter particular risk or protective mechanisms rather than overall functioning. However, microtrials use interventions that are more extensive than the brief presentation of individual stimuli used in laboratory studies. For example, Hariri et al. (2002, 2005) provided an excellent example of a laboratory study of risk mechanisms. They first genotyped participants, then randomly assigned them to experimental conditions where faces with angry or neutral expressions were presented. During the presentation brain activation was assessed using functional MRI. The researchers found that participants carrying the short 5-HTTLPR allele had stronger amygdala response to emotional faces than did those with the long allele. These findings, combined with other research on amygdala response during depressive episodes, support an etiologic theory of depression that includes genetic moderation of emotional response. However, the findings do not indicate whether these risk mechanisms might be malleable targets for preventive interventions. A genetically informed microtrial design building on Hariri et al. (2005) might begin where the experimental study ended. Such a design would systematically introduce and evaluate the efficacy of intervention components that could increase the capacity of persons particularly prone to emotional responses in aversive social situations to regulate those responses.

Unlike laboratory studies, which often focus on transient responses, microtrials can also be designed to bring about moderately stable changes in risk or protective mechanisms that continue beyond the brief period of exposure to the experimental condition. Microtrial designs can build in longer follow-up periods on the order of weeks or months to assess both the degree of change in risk or protective mechanisms and the stability of that change. Microtrials also borrow important design elements from full-scale randomized prevention trials. As noted

previously, experimental manipulations used in microtrials can parallel, in more limited fashion, components of larger prevention trials. This can include intervention formats, such as workshop exercises, as well as intervention content. The study by Fishbein et al. (2006) used a group facilitation format similar to that used in large-scale prevention trials and selected specific content that had been used with adolescents in these larger programs.

Microtrials also differ substantially from standard trials of preventive intervention programs. Standard programs are complex, multifaceted, and designed to change distal outcomes by influencing a variety of risk or protective factors, under the assumption that significant intervention effects will be multiply determined. Microtrials are much briefer and focus on changing a limited set of risk or protective mechanisms as an initial test of malleability prior to incorporating them as targets in full-scale programs. For example, Fishbein et al. included measures of specific social competencies hypothesized to influence risk for more distal problems such as involvement in violence. As a result, microtrials are much less expensive and time consuming than full-scale trials and provide more limited, but precise, information on the malleability of specific mechanisms.

Finally, microtrials borrow design elements from passive longitudinal field studies designed to test models of risk and protective mechanisms as they unfold over time. As with field studies, microtrials include careful measurement of such mechanisms and can use short-term longitudinal designs to track stability and change. At the same time, microtrials differ from passive longitudinal field studies in several ways. Because microtrials incorporate experimental designs with random assignment to controlled environmental manipulations, they can rule out potential confounds that passive field studies can miss. Random assignment has the advantage of ruling out plausible rival hypotheses that can be mistaken for environmental effects in longitudinal correlation research designs, such as history (unmeasured environmental events that co-occur with measured events), maturation (natural change with time), repeated testing (prior assessments change responses to subsequent assessments), and statistical regression (initial low or high assessments will shift toward the population mean on subsequent assessments) (Shadish et al. 2002).

Microtrials and Gene-environment Interaction

Genetically Informed Microtrials

In the most basic prototype for a genetically informed microtrial, participants would provide DNA samples and be randomly assigned to one of at least two experimental conditions. One condition would involve participation in a standardized set of experiences hypothesized to increase rates of a putative protective factor or decrease rates of some risk factor. The second condition would involve either a no-exposure control condition or a comparison condition designed to control for nonspecific aspects of exposure. The targeted risk or protective factor would be measured before and after participation, with a follow-up assessment a few weeks later to test stability of effects.

This basic prototype can be enhanced in several ways, depending on study goals and resources. Two-stage sampling with immediate genotyping and stratified assignment based on genetic variants would increase power to detect interaction effects when important variants occur at relatively low frequency in the population. More than one experimental condition can be used to determine whether change mechanisms have different effects on participants with different genetic variants. Intensity or dosage of the experimental condition can be varied to determine whether malleability requires a threshold level of intervention. Two or more risk or protective factors can be assessed to determine whether effects are unique or generalize to people with different genetic variants.

Design Advantages of Microtrials

Genetically informed microtrial designs have several advantages, including enhanced statistical power, the capacity to identify or rule out spurious risk or protective factors, and the capacity to study low-frequency environments or genetic variants.

First, genetic moderation of intervention effects may be more easily detected using microtrial designs. Tests of moderation are commonly underpowered for several reasons. Within-group variation in exposure to intervention often adds error variance to intervention condition, and this is more likely to occur with complex multisession interventions. Power to detect interactions is also reduced when categorical predictors are not equally distributed across categories, a common situation when studying genetic variation. Comprehensive measurement of risk or protective factors is often limited by practical considerations, reducing reliability in the measurement of outcomes and further decreasing power to detect effects.

These problems can be overcome in microtrial studies, which feature standardized environmental manipulations, oversampling to achieve equal proportions of genetic variants, and intensive measurement of specific risk or protective mechanisms. McClelland and Judd (1993) demonstrated that low residual variance in the product terms of interacting variables contributed to low power to detect significant interaction effects in longitudinal correlational research. In contrast, experimental designs were dramatically superior in the detection of moderator effects. McClelland and Judd also found that correlational designs had less than 20% of the efficiency of experimental tests, using similar measures in detecting interactions. Consequently, the introduction of experimental designs in the form of microtrials can increase statistical power to detect GxE effects as much as five fold.

Second, microtrials are useful in studying risk or protective mechanisms that occur relatively infrequently and are not amenable to assessment through field studies. Microtrials can create environmental conditions that are uncommon in daily life and oversample low base rate genotypes to provide designs with greater power to detect effects. This is particularly important when studying the contributions of specific gene variants that occur at low frequency in the population. For example, we have just begun a microtrial with a first-stage assessment that includes obtaining saliva samples by mail, in order to genotype for the serotonin transporter gene, allowing us to randomly assign individuals to experimental or control groups in equal numbers across the three different allele groups. We estimate that we will need to oversample by a factor of 2.5 to obtain equal groups, using this relatively economical first-stage screening method.

Third, because they employ experimental designs with full randomization, microtrials can rule out a number of alternative rival hypotheses about risk and protective mechanisms that are difficult to evaluate using passive longitudinal designs. To date, the development of preventive interventions has been based on the assumption that associations found between environmental risk factors and various outcomes are due to the environment causing the outcome. Recent evidence shows that associations of some environmental risk factors with outcomes may be, in part, genetically mediated. Passive gene-environment correlation constitutes one possible form of genetic effect, particularly when the putative risk factor involves the family environment. Passive G-E correlation occurs when both the environmental risk factor and the outcome are shaped by common genes shared with family members who contribute to the social environment of the target individual. Evidence for passive G-E correlation comes from behavior genetic studies. For example, Plomin et al. (1994) found in a combined twin and adoptive sample that over a quarter of the variance in parenting and family environment measures could be accounted for by genetic differences among children. If passive G-E correlation does, in fact, account for associations between particular social environments and the development of disorder, then prevention efforts targeting those social environments may

require a different approach than they would if the causative social environments were independent of genetic variation. In this case as well, microtrials, which randomly assign target individuals to different social environments, can rule out confounds due to passive G-E correlations. Two designs are possible. Interventions can be designed to work specifically with children or adolescents, similar to the design employed by Fishbein et al. An alternate design would target the child's existing environment, using an intervention such as a single parent training workshop. If the child is not involved in the intervention in any way, then subsequent changes in child behavior must be a function of changes in the child's social environment brought about by the intervention.

Microtrials can also be used to test and rule out another pattern of G-E correlation that can distort the results of passive longitudinal field studies. Genetic influences extend to individual differences in exposure to life circumstances, such as harsh parenting or stressful events that are assumed to be risk mechanisms for many important outcomes of interest to prevention researchers. Effects of genetics on life circumstances arise because people's behavior shapes and selects their environments and influences others' responses to them (for example, a temperamentally rambunctious child can elicit harsh, controlling parenting). Termed *evocative G-E correlation*, such effects involve a reversal of the assumed causal order, with behavior shaping the social environment rather than the environment shaping behavior (Narusyte et al. 2008). Again, microtrial designs can control for or examine hypothesized evocative G-E effects, providing direct evidence concerning direction of effect and information relevant to enhancing the power of preventive interventions.

Even when correlational field studies find evidence for gene-environment interaction, it is possible that these findings mask effects that may become apparent when probed using microtrial designs. For example, when two potentially causative environments covary, as when economic hardship is associated with harsh parenting, correlational designs may provide little basis for distinguishing the alternative models. As a result, the finding that one environmental factor interacts with genetic variation in predicting an outcome may actually be carrying information about a different, unmeasured environmental factor. Microtrials can test whether altering one environmental factor has genetically varying effects on a key risk process, ruling out the effects of other environmental factors that are not manipulated, and substantially clarifying the interpretation of the observed interaction effect.

A G-E interaction may also hide a gene-gene interaction, if the environmental factor is part of a passive G-E correlation. For example, if harsh parenting is associated with parental genes, then variation in parenting indirectly carries information about child genes, and correlational evidence that harsh parenting interacts with child genes in predicting child adjustment might also be accounted for by gene-gene interaction. A microtrial targeting this environmental factor and demonstrating genetic moderation of effects would again allow us to rule out such an interpretation.

Microtrials as Follow-ups to Genetically Informed Prevention Trials

Although we have focused primarily on microtrials as bridges from basic to applied research, we believe they can also play a seminal role in refining existing prevention programs that have already been tested in full-scale randomized field trials. We need to understand why some individuals do not benefit from existing prevention programs, and to design new programs that are effective for these individuals. Microtrials can contribute to this work.

First, microtrials can test which existing intervention components are less effective, and whether effectiveness varies across groups of individuals or across general contexts. This can be accomplished in a number of ways. Microtrials can be conducted with new samples, as Fishbein et al. (2006) did. Microtrials can also be a planned extension of a randomized

prevention trial, using a “trial within a trial” design (Brown and Liao 1999) to study the effects of new intervention components on a small randomly selected set of participants who fail to show immediate changes in key mediators as a result of the full-scale intervention. Microtrials can also be integrated with established community-based prevention programs to test new intervention components for those participants who show no change in important mediators. Findings from these designs can be useful in developing programs that integrate both universal and selective interventions into a continuum of service.

Second, genetically informed studies may provide guidance in identifying combinations of risk and protective mechanisms that need to be targeted through different intervention components, and microtrials can be used to test the effects of these novel components before they are integrated into a revised full-scale program. Microtrials can also be used to extend findings of genetically informed full-scale prevention trials such as the Brody et al. study described earlier. To the extent that identifiable risk and protective mechanisms can be shown to mediate the impact of an observed GxE effect on prevention outcomes, these mechanisms can become the target of adaptive designs or multi-tiered intervention programs. Focusing on plausible mechanisms is more easily done in the context of microtrials than in either basic laboratory studies or in preventive intervention trials. At the same time, a focus on “risk processes” has the potential to identify correctly a greater proportion of individuals “at risk” while maintaining a focus on malleable points of potential intervention. This highlights the critical role of microtrials in turning an observed GxE effect into new, useful targets for preventive intervention.

Challenges in Using Microtrials

Strength of Effect

The full range of application for microtrials has yet to be explored and will be shaped by several important challenges. First, environmental manipulations used in a microtrial must be strong enough to bring about significant change in important mediators. For example, Gottman et al. (2005) used a microtrial design to study changes in couples’ interaction as a result of several different focused manipulations involving components of workshop materials from a program designed to improve couples’ communication. These included a component to enhance a couple’s friendship, a component to teach couples how to regulate conflict, a two-day workshop involving both components, and a bibliotherapy condition in which couples received a book on communication. As predicted, the two components had somewhat different effects on specific dynamic characteristics of observed couple interaction that were considered to be important risk factors for marital distress, but other effects emerged only when both components were included. This study demonstrates that microtrials can be enhanced by comparing both individual components and combinations of components, or by including exposure to various dosages of a particular component. These methods can provide data on the strength of an intervention component or set of components necessary to bring about change. The effects of components or of dosage may also vary for different individuals, suggesting that genetically informed microtrials can provide important insights concerning these issues as well.

Maintenance of Change

Microtrial studies must also address the challenge of how to maintain changes once they occur. This will require that theories of risk and protection devote more attention to the mechanisms that lead to stabilization and maintenance of protective factors. For example, studies of parent training programs suggest that these programs are less effective among parents with depression (Dumas et al. 1989) or parents in conflicted marriages (Webster-Stratton and Hammond 1990). Microtrials comparing focused parent training sessions for parents with or without depression may provide important data indicating whether the programs’ reduced effectiveness

is due to a lack of initial effects or to quick fading of effects, and why this might be. Likewise, inclusion of possible genetic moderators has the potential to explicate different pathways of change maintenance as a function of individual differences.

The issues of dosage and maintenance are likely to become more salient if etiologic research identifies correlated constraints or self-maintaining systems. Correlated constraints involve risk factors that are likely to co-occur and may influence one another (Gest et al. 1999). For example, marital conflict may spill over into parent-child interaction through parental irritability (Jouriles and Farris 1992), or economic hardship may increase depression and reduce both time and energy to invest in new parenting strategies (Ge et al. 1992, 1995). In such cases, microtrials may reveal that specific risk mechanisms can be changed, but that change is limited and fleeting when other correlated conditions intrude. This would call for alternative intervention strategies to address the problem of multiple constraints. Such findings can thus inform the development of more complex multi-component or adaptive interventions needed to bring about more lasting change because several components are required to reach a threshold at which intervention effects can be maintained.

Self-maintaining systems are a more complex example of correlated constraints. Such systems involve bidirectional influences among system variables that lead to stabilization of the system within a particular configuration. For example, Gottman et al. (2005) provided evidence that mutual influence during couple interaction can constrain couples' behavior within a very limited range, either positive or negative. These data suggested that only certain intervention components had any effect in helping couples into a more positive steady state, which Gottman et al. suggested would become self-perpetuating. Self-maintaining systems may also reflect active gene-environment correlation resulting in systemic problems that escalate and become self-perpetuating (O'Connor et al. 1998; Reiss et al. 2000). Again, inclusion of genetic variables in such models may help to provide a physical basis for indexing some important parameters in dynamic system models, thus enhancing their potential to guide decisions about prevention programming.

Microtrials may be particularly useful for dynamic system models that identify control parameters thought to determine which of several behavioral patterns a system stabilizes around. For example, Alexander and Barton (1980) found that briefly manipulating motivational set (cooperative vs. competitive) led to substantial changes in the observed interaction of families with delinquent children, such that their interactions in the cooperative condition were indistinguishable from those of control families. This suggests that motivational set may act as a system control factor, with changes in set leading to discontinuous change in behavior.

Limitations of Microtrials

Microtrial methods will clearly have limits, and we have noted several likely limiting conditions. There will be many situations where risk or protective mechanisms can only be changed through high dosages or multiple component interventions to address a range of correlated constraints. However, given the general absence of empirical tests of the malleability of risk and protective mechanisms currently targeted in preventive interventions, we believe it will be profitable to test these limits, rather than assume them.

Ethical Issues

Investigators planning microtrials also must consider ethical issues unique to this research design. Laboratory studies are designed with no expectation that participants will benefit or that the effects of the experience will persist; intervention trials are designed with both expectations. Microtrials are designed in such a manner that participants may receive limited

benefits that may persist for some time, but the goal of the study is to test theories of change rather than to bring about such benefits. As a result, informed consent procedures must clarify these goals and expectations, which may be unfamiliar to potential participants and to institutional review boards. This will be of particular importance when microtrials are used to inform indicated prevention programs that target individuals showing early danger signs for substance use or psychopathology. In these cases, as in situations using microtrials to inform treatment of existing conditions, investigators must consider two additional human subjects protections. Research protocols will need to include methods for identifying potential immediate iatrogenic effects of the program component, and will need to build in procedures for timely referral for treatment.

The Issue of Genetic Screening

It may be tempting for some to argue that cost savings and efficiency are best achieved by designing selective preventive interventions for children and youth with particular genetic constellations considered to place them at risk for distal outcomes such as conduct disorder, depression or binge drinking. Our approach to this issue is framed by both basic science of developmental psychopathology and public health considerations.

Considering the current state of findings on gene-environment dynamics, single genes or single GxE combinations do not account for enough variance in distal outcomes to support screening for intervention. There are likely to be multiple developmental pathways to behavioral health, each shaped by multiple factors. Genes are more likely to constrain or enhance various pathways than shape final outcomes, in part because the same genetic constellation may constrain a pathway in one context and enhance the same pathway in another. Interventions that promote adaptability and resilience during childhood and adolescence increase the number of pathways available for an individual (Brody et al. 2009a, b; Luthar 2006). For example, children high on emotional reactivity may develop fewer internalizing problems if they also gain skill in emotion regulation (Degnan and Fox 2007). Given the dynamic multivariate nature of development, we maintain that genetic screening for selective intervention will provide few benefits in advancing prevention efforts. We also advocate for incorporating genetic information in the study of specific risk and protective mechanisms and how they might be better shaped, in order to integrate selective intervention components within universal intervention programs designed to promote resilience.

Conclusions

We have suggested that microtrials are an underutilized and cost-effective means of translating basic research findings into promising preventive interventions. We regard microtrials as a particularly promising method of applying the burgeoning research into gene-environment dynamics to advance prevention science and enhance the effectiveness of prevention programs. We view microtrials as a key method of identifying malleable risk and protective mechanisms that can serve as central targets for adaptive interventions geared to provide more effective services to a wider range of participants, through the integration of universal and selective interventions.

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Fig. 1.
The translational role of microtrials in the preventive intervention research cycle

Table 1

Design elements and relative advantages of microtrials in comparison to other designs

	Laboratory studies	Correlational field studies	Microtrials	Full-scale randomized trials
Sampling				
Oversample low baserate protective conditions or gene variants	X		X	
Intervention				
Target specific risk/protective mechanisms likely to differ across genes	X		X	
Specify and control environmental conditions likely to moderate genetic associations	X		X	
Use intervention formats in constructing experimental conditions			X	X
Experimentally compare intervention component effects on risk/protective mechanisms			X	X
Design				
Rule out confounds using random assignment	X		X	X
Rule out reverse causal effects, including G-E correlation	X		X	
Increase power to detect GxE interactions in smaller samples	X		X	
Assessment				
Conduct comprehensive standardized assessment of risk/protective mechanisms	X	X	X	
Assess longer-lasting change in risk/protective mechanisms		X	X	X
Other				
Reduce costs of translational research			X	
Experimentally examine novel interventions to increase effectiveness of existing prevention programs			X	