

Revisiting Pasteur's Quadrant: Use-Inspired Basic Research

Science of Behavior Change Common Fund

National Institutes of Health

OCTOBER 9-10, 2012

Meeting Report

Revised March 4, 2013

This summary report was prepared by Chandra Keller-Allen, Rose Li & Associates, Inc., under contract to the National Institutes of Health, HHSN271201200740P. The statements, conclusions, and ideas contained in this document reflect both individual and collective opinions of the meeting participants and are not intended to represent the official position of the National Institutes of Health or the U.S. Department of Health and Human Services. We gratefully acknowledge review of and comments on earlier drafts of this report provided by Nader Amir, David Barlow, Warren Bickel, Richard Bootzin, Michelle Carlson, Robert DeRubeis, Edna Foa, Allison Harvey, Stefan Hofmann, Jonathan W. King, Rose Maria Li, David MacKinnon, Inbal Nahum-Shani, Joseph Newman, Lisa Onken, George Rebok, Timothy Strauman, Nancy Tuvesson, Kevin Volpp, and Robin Weersing.

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Executive Summary

Purpose

There have been concerted attempts to bridge basic and applied disciplines with multiple interdisciplinary initiatives at the National Institutes of Health (NIH). However, major gaps between basic and applied science still exist in the field of behavior change. Perhaps even more concerning is the gap between efficacy and effectiveness research. More often than not, interventions deemed efficacious fail to be effective. The costs of this efficacy-effectiveness gap are enormous for NIH, but more importantly for public health.

The Science of Behavior Change (SOBC) Common Fund program convened a meeting to explore how use-inspired basic research as a component of intervention research can help to close this gap. *Revisiting Pasteur's Quadrant: Use-Inspired Basic Research* examined how basic science questions about how behavioral interventions work can be asked within applied or clinical research studies on these interventions. The proximal goal of such research is to determine how an intervention exerts its effects, with the ultimate goal of modifying the intervention to become more potent, streamlined, efficient, and implementable. Specifically, this meeting explored how to conduct basic research—within the context of intervention studies—so that efficacious but difficult-to-implement interventions can be modified to be implementable, community-friendly interventions that work in the existing health care delivery system.

The meeting consisted of three panels of presentations from researchers in the field addressing integration of use-inspired basic research into (1) research on intervention generation and refinement, (2) research on intervention efficacy, and (3) research on effectiveness and implementation. A fourth panel addressed methodology for testing mechanisms of action. Each panel was followed by a facilitation discussion among meeting participants.

Research on Intervention Generation and Refinement

The panel on intervention generation and refinement focused on very specific mechanisms in the areas of social anxiety, psychopathy, addiction, insomnia, depression, and bipolar disorders. The work on mechanisms presented in these areas provides enormous potential for simple, effective, and implementable interventions that target specific mechanisms. There are multiple ways to proceed with research depending on the state of science for various disorders. Focusing on the micro-intervention level at each stage allows for examining mechanisms.

Research on Intervention Efficacy

The panel on intervention efficacy demonstrated the necessity of understanding the components of an intervention in order to make scientific advances. Presentations included an informative history of exposure therapy and related advances in anxiety disorder treatments,

the use of D-Cycloserine for boosting the effects of an intervention, and the role of sudden gains and therapeutic alliance in cognitive behavioral therapy (CBT).

Expanding Methods for Testing Mechanisms of Action

The methodology panel described exciting and innovative research designs and strategies for examining mediators and mechanisms. Presentations included explanation of factorial designs, sequential, multiple assignment, randomized trials, methods for mediation analysis, idiographic methods, and single-case experimental designs. These alternative designs allow for honing in on mediators, mechanisms, and identifying effective components of complex interventions.

Research on Effectiveness and Implementation

The last panel addressed the challenging topic of incorporating basic science into effectiveness research. Panel members presented their perspectives on balancing competing demands in effectiveness research, adaptive randomization models, and testing mechanisms within effectiveness trials.

Future Directions

The mechanisms discovered today are the levers for interventions of tomorrow. Participants in this meeting were excited to explore methods of testing mechanisms by using innovative designs, collaborating across disciplines, and focusing on various stages of intervention development and implementation with the goal of designing effective, implementable interventions targeting specific mechanisms of behavior change. It is hoped that this discussion represents the beginning of further collaboration and discussion on improving outcomes in real-world treatment for a variety of disorders.

Introduction

There have been concerted attempts to bridge basic and applied disciplines with multiple interdisciplinary initiatives at the National Institutes of Health (NIH). However, major gaps between basic and applied science still exist in the field of behavior change. Perhaps even more concerning is the gap between efficacy and effectiveness research. More often than not, interventions deemed efficacious fail to be effective. The costs of this efficacy-effectiveness gap are enormous for NIH, but more importantly for public health.

The Science of Behavior Change (SOBC) Common Fund program convened a meeting to explore how use-inspired basic research as a component of intervention research can help to close this gap. *Revisiting Pasteur's Quadrant: Use-Inspired Basic Research* examined how basic science questions about how behavioral interventions work can be asked within applied or clinical research studies on these interventions. The proximal goal of such research is to determine how an intervention exerts its effects, with the ultimate goal of modifying the intervention to become more potent, streamlined, efficient, and implementable. Specifically, this meeting explored how to conduct basic research—within the context of intervention studies—so that efficacious but difficult-to-implement interventions can be modified eventually to be implementable, community-friendly interventions that work in the existing health care delivery system.

There are three basic problems in this area: (1) major gaps between basic and applied behavioral science; (2) an efficacy-effectiveness gap (i.e., often, efficacious interventions are not effective); and (3) efficacious behavioral interventions that may never be implemented. Invited speakers and audience members were asked to consider how use-inspired basic research (i.e., mechanisms of behavior change) as a component of behavioral intervention development research can serve to address these problems and close the gap between basic and applied research. The goal is for basic research to inform behavior intervention development in order to make interventions more implementable. This meeting sought to explore how use-inspired basic science questions of mechanism can be asked within each stage of behavioral intervention development research, address practical goals in addition to advancing basic science knowledge, and boost the effects of behavioral interventions.

The work of Louis Pasteur, whose studies of bacteriology were carried out at the behest of the French wine industry, characterizes the work of basic scientists (e.g., Niels Bohr) searching for fundamental knowledge who select their questions and methods based on potential relevance to real-world problems.¹

¹ Stokes, D. E. (1997). *Pasteur's Quadrant: Basic Science and Technological Innovation*. Washington, DC: Brookings Institution Press.

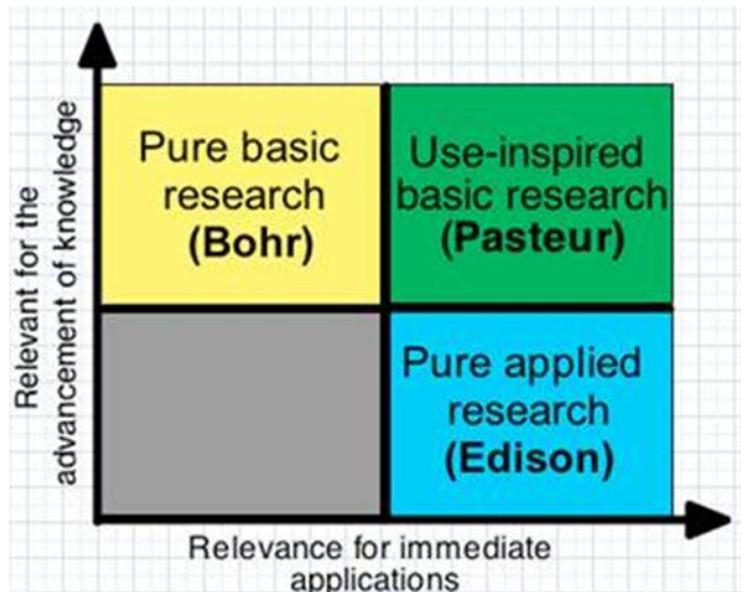


Figure 1. Pasteur's quadrant

The meeting agenda included three panels of speakers that focused on different stages of intervention development: (1) research on intervention generation and refinement; (2) research on intervention efficacy; and (3) research on effectiveness and implementation. A fourth panel addressed expanding methods for testing mechanisms of action.

Meeting organizers charged the participants to examine if and how use-inspired basic research can be conducted at each stage of research, identify the obstacles to doing so and whether and how the obstacles can be overcome, explore relevant methodological strategies that could enable use-inspired basic research at each stage, and provide input on how basic science can be integrated into applied behavioral science.

Incorporating Use-Inspired Basic Research into Research on Intervention Generation and Refinement

Modification of Attention Bias: A Novel Treatment for Anxiety Disorders

Nader Amir, PhD, San Diego State University

Information processing models of anxiety suggest that anxious individuals focus their attention on threat-relevant information. Reviews of studies of attention bias in anxiety using the probe detection task have shown that individuals with generalized anxiety disorder have an attention bias for threat that is absent in non-anxious controls² and that attention bias in anxiety is

² Mogg, K., & Bradley, B. P. (2005). Attentional bias in generalized anxiety disorder versus depressive disorder. *Cognitive Therapy and Research*, 29, 29-45.

consistent and reliable.³ Attention bias may be one cause of anxiety, and therefore reduction of attention bias should lead to a reduction in anxiety.

Attention Training to Reduce Response to a Stressor

The first goal of Dr. Amir's research was to discover if attention training can reduce response to a stressor (e.g., public speaking challenge). Methods for measuring attention were borrowed from basic cognitive research and involved measuring response time to various images of differing emotional valance. In the attention modification program, the probe follows a neutral face on 80 percent of trials. In the attention control condition, the location of the probe is random and not related to the location of the emotional face. Both conditions include 160 trials with varying probe types (E or F), probe position (top or bottom of screen), and emotion types (threat or neutral).

Study participants were 105 individuals with social anxiety randomly assigned to the attention modification program (n = 51) or the attention control condition (n = 54). Anxiety was assessed at three time points—pre-training, post-training, and post-challenge—using the State-Trait Anxiety Inventory (STAI). The modification program was intended to change participants' response to stress, not change the underlying anxiety. To test the effect of attention training, Dr. Amir used the Posner paradigm that is intended to measure the ability to disengage attention from negative stimuli. The post-training challenge given to participants was to deliver a videotaped 5-minute speech on a self-selected topic that was rated by observers for quality.

Results indicated that those who had training learned to focus their attention away from threat. Baseline and post-training measures of state anxiety did not differ. However, those who had training had less anxiety after the speech challenge. Moreover, independent observers considered the speeches given by those who were in the modification program to be better than the speeches given by those who were in the control group.⁴ The investigators replicated the study several times to confirm the results.

Mediation Analyses

Dr. Amir and his colleagues conducted mediation analyses using MacKinnon's procedure⁵ to test the product of the coefficients to determine whether the anxiety modification program exerted its influence through change in attention bias to threat. This intervention has a unique advantage because it is possible to specify the variable that is responsible for change and to examine its effect on the outcome variable of interest. The product of two coefficients is

³ Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. *Psychological Bulletin*, 133, 1-24.

⁴ Amir, N., Weber, G., Beard, C., Bomyea, J., & Taylor, C. (2008). The effect of a single session attention modification program on response to a public speaking challenge in socially anxious individuals. *Journal of Abnormal Psychology*, 117, 860-868.

⁵ MacKinnon, D. P., Fairchild, A. J., & Fritz, M. S. (2007). Mediation analysis. *Annual Review of Psychology*, 58, 593-614.

calculated: the independent variable (modification program versus control group) to the mediator (attention bias after training); and the mediator (attention bias after training) to the dependent variable (change in state anxiety scores from pre- to post-speech and speech performance) when the independent variable is taken into account.

The MacKinnon mediation test is a variation on the Sobel test that accounts for the non-normal distribution of the indirect path. When the 95 percent confidence interval of the indirect path ($\alpha\beta$) does not overlap with zero, it indicates mediation. In this analysis, the results indicated that neither of the confidence intervals for change in state anxiety [0.015, 0.203] or observer-rated speech performances [0.004, 0.166] crossed zero. A second study training attention away from contamination-related materials in participants with obsessive-compulsive disorder (OCD) symptoms yielded the same results.⁶

Attention Training Intervention as Treatment

The second goal of Dr. Amir's research was to determine if an attention training intervention could be used as an effective treatment for anxiety disorders in a randomized controlled trial (RCT).⁷ Participants in the RCT met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for social anxiety disorder as their primary diagnosis and were randomly assigned to the attention modification program (letter E or F followed a neutral face on 80 percent of the trials) or the attention control program (letter E or F followed neutral and threat faces with equal probability). Training sessions were completed in the laboratory two times per week for 4 weeks.

At the end of the trial, 50 percent in the treatment group did not meet the disorder criteria. However, basic questions of efficacy are by themselves inadequate. It is important to determine why particular treatments work better for some individuals than others and what should be done with people who do not respond.

Identifying Predictors of Treatment

Identifying predictors of treatment response can be methodologically challenging. Prognostic variables, which predict outcomes irrespective of treatment, and prescriptive variables, which predict differential treatment response between two or more treatment conditions, are both pre-treatment variables that have predictive utility. These predictors are often identified during post hoc analysis and are typically disconnected from theory. Also, variability in treatment procedures and delivery across studies can be problematic in identifying predictor variables.

⁶ Najmi, S., & Amir, N. (2010). The effect of attention training on a behavioral test of contamination fears in individuals with subclinical obsessive-compulsive symptoms. *Journal of Abnormal Psychology, 119*, 136-142.

⁷ Amir, N., Beard, C., Taylor, C., Klumpp, H., Elias, J., Burns, M., & Chen, X. (2009). Attention training in individuals with generalized social phobia: A randomized controlled trial. *Journal of Consulting and Clinical Psychology, 77*, 961-973.

The gold standard in determining efficacy is the RCT; however, this design provides inadequate information about mechanisms.

Exploratory analyses were conducted in the group of participants receiving the attention modification program to identify potential predictors of response to this intervention. Potential predictor variables for this particular study can be found by examining prior research on the mechanisms of action in the attention modification program, contemporary information processing models of social phobia,⁸ or previous research examining predictors of treatment response in social phobia.⁹ The variable domains included cognitive disturbance factors (e.g., attention bias for threat, social interpretation bias), clinical characteristics (e.g., social anxiety severity, depression), and demographics and life circumstances (e.g., age).

The exploratory analysis to identify potential predictors of treatment response for participants receiving the attention modification program showed that all variables were significant predictors at the univariate level. The most robust predictor in the overall model was the attention bias score. Specifically, greater difficulties disengaging attention from social threat cues at week 1 predicted superior response to the attention modification program, even when statistically accounting for baseline Liebowitz Social Anxiety Scale (LSAS) scores.¹⁰

Future Research

Future work will include research on treatment selection (computer training versus cognitive behavioral therapy), treatment augmentation in different settings, identifying better methods of changing bias, and identifying better predictors of response (e.g., inhibitory learning based on contemporary learning principals).

Question and Answer

In the first experiment, the 50 percent of participants who did not respond to the attention modification program all met general criteria for anxiety disorder. Comorbidity does not appear to be a good predictor of treatment response.

It would be interesting to explore how attention bias fits in with other cognitive biases (e.g., interpretation bias) in anxiety disorders, which could be another future direction for research. Dr. Amir noted that he is conducting parallel research in memory training with positive results.

⁸ Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology, 1*, 167-195.

⁹ Hofmann, S. G. (2000). Treatment of social phobia: potential mediators and moderators. *Clinical Psychology: Science and Practice, 7*, 3-16.

Rodebaugh, T. L., Holaway, R. M., & Heimberg, R. G. (2004). The treatment of social anxiety disorder. *Clinical Psychology Review, 24*, 883-908.

¹⁰ Amir, N., Taylor, C. T., & Donohue, M. C. (2011). Predictors of response to an attention modification program in generalized social phobia. *Journal of Consulting and Clinical Psychology, 79*, 533-541.

A combination of these interventions is likely to be the most effective. Attention bias is considered a gatekeeper to the information processing system.

The effects of the intervention were retained at a 1-year follow-up.

These treatments could impact comorbidities. In the generalized anxiety study, the results also seem to translate for depression. More studies on this question are needed; Dr. Amir and colleagues are currently looking at comorbid substance abuse and overeating.

There is currently no information about the predictors of the maintenance effects of treatment. Dr. Amir has collected anecdotal information through interviews. It appears as though the training may change some kinds of early processes that have long-term effects.

Matching Cognitive Remediation Training to the Differential Deficits of Psychopathic and Externalizing Prisoners: Specifying the Mechanisms of Action

Joseph Newman, PhD, University of Wisconsin

Dr. Newman and his colleagues have been working for several years to identify and specify the mechanisms operating in psychopathic and externalizing patients. The hope is that by understanding these mechanisms, treatment can be tailored to the specific deficits that impact these individuals, leading to changes in their often costly and disinhibitory behavior. He coined the term “disinhibitory psychopathology” 30 years ago to describe a latent construct of a predisposition to a group of disorders that ran in families. It is associated with impulsive disinhibited behavior, conduct disorder, attention deficit hyperactivity disorder (ADHD), substance abuse, and criminal behavior. The unifying theme is the failure to self-regulate; however, it manifests with diverse etiologies.

Two Distinct Subgroups: Psychopathy and Externalizing

From a clinical perspective, disinhibitory psychopathology is important because it is strongly associated with substance abuse and criminal behavior. Risk for these problems reflect an underlying deficit in self-regulation. The original hypothesis was that this was a unified group. However, it was discovered through laboratory studies that two distinct subgroups within individuals display disinhibitory psychopathology: psychopathy and externalizing traits. These two subgroups differ phenotypically and etiologically. Psychopathy includes interpersonal/affective (e.g., superficial charm, grandiosity, lack of empathy) as well as impulsive antisocial behaviors (e.g., premeditated aggression). A combination of these traits can lead to substance abuse disorders and criminal behavior. Externalizing traits include impulsivity and conduct problems that lead to substance abuse and criminal behavior and are more likely to display reactive aggression.

Distinct mechanisms of action operate within psychopathy and externalizing individuals. With psychopathy, an early attention bottleneck disrupts information processing. The early bottleneck filter circumvents executive function, because there are fewer conflicts or cognitive

demands. As a result of this attention bottleneck, affective information does not influence behavior or decision-making. This path leads to disinhibited behavior because individuals cannot attend to contextual information. The mechanism of action for externalizing traits involves an over-allocation of attention to motivationally significant information. As a result fewer resources are available for executive function. This disinhibited and poorly regulated attention and executive function response yields increased emotion response. This path leads to disinhibited behavior because individuals cannot apply affective cognitive control to regulate maladaptive responses.

Mechanism-Specific Treatment Pilot RCT

Individuals with disinhibitory psychopathology are considered very difficult to treat or treatment resistant. However, this may reflect the fact that existing treatments do not target the underlying deficits. It may be necessary to address cognitive deficits interfering with regulation in order to receive the benefit of other interventions. Cognitive remediation is ideally suited to address these deficits. Dr. Newman's study seeks to develop a cognitive remediation treatment program that trains particular skills, such as paying attention to contextual cues for psychopathic individuals and applying working memory and attention to strengthen affective cognitive control for externalizing individuals.

Dr. Newman and colleagues conducted a pilot study in order to demonstrate these basic science ideas at work within a specific population. The primary aim of the pilot was to determine if it is possible to change disorder-specific deficits and demonstrate the specificity of change in relevant laboratory measures. The goal of treatment for individuals with psychopathy was to notice and make use of important information in order to address the deficient mechanism of attention to contextual information. The goal of treatment for individuals with externalizing traits is to train them to act rather than over-react in emotional situations in order to address the deficient mechanism of affective cognitive control.

The pilot study population ($n = 60$) was drawn from substance dependent prisoners and identified as either displaying psychopathy or externalizing traits. Half were randomized to the treatment designed for the mechanism of action of their subgroup (psychopathy or externalizing), and half were randomized to the treatment that does not match their subgroup (mismatch). Pre-treatment and post-treatment sessions were conducted to assess mechanism-related deficits. Some of these measures were selected to assess the deficits of the externalizing group (N-Back, paced auditory serial addition test, and instructed fear), whereas others were selected to address deficits of the psychopathy group (a modified Stroop test, lexical decision, and instructed fear). The pre- and post-treatment measures were intended to evaluate the specificity of the etiological deficits and determine if specific change can be brought about in the mechanisms being addressed by these laboratory measures. Participants engaged in six training sessions consisting of three computerized tasks per treatment that train for mechanism-related skills. Training for psychopathy deficits included the reversal, context discrimination, and gaze tasks to strengthen attention to contextual cues. Training for externalizing deficits included breath holding, go-stop task, and the Simon task to address

acting without overreacting. The hypothesis was that there would be minimal change between pre- and post-measures for participants who were mismatched to treatment.

Preliminary Results and Next Steps

Preliminary results of the pilot demonstrate significant improvement between pre- and post-training on multiple outcome measures for individuals whose subgroup (psychopathy or externalizing) was matched to the specific skills training in the intervention and no change for those who were mismatched. The strength of the study design of two treatments and two disorders fully crossed eliminates the possibility of alternative interpretations and allows the researchers to concentrate on mechanisms of action. There is a clear syndrome-specific link between obtaining the correct treatment and experiencing etiologically relevant change. These preliminary results are quite promising because training-related changes in behavior generalize to independent assessments of the targeted deficits (i.e., different tasks). Furthermore, they are not just arbitrary tasks; they are etiologically relevant tasks and, particularly with the findings for psychopathy, the change is seen in multiple measures.

The team continues to collect cohorts and will be able to complete a more sophisticated analysis with a larger sample size. Next steps include additional statistical analyses (structural equation modeling) and analysis of changes in brain activity. Future work may include a community-based follow-up, a comparison to treatment-as-usual among the prison population, and refining and strengthening of the training regimen.

Question and Answer

There are many motivations for the prison population to participate in the study. The training affords them something to do in an otherwise monotonous environment, and they are paid for their participation based on task performance. There has been very low attrition, and participants typically only drop out due to administrative segregation.

This work is iterative and incremental. The checklist used to identify psychopathy versus externalizing is a great instrument, but it is also possible that some individuals are misclassified. As the work continues, the research team will experiment with using the pre-treatment measures to verify classification in order to refine analysis of the treatment effects.

The characteristics of psychopathy and externalizing traits were well delineated, and it is clear the groups differ in emotional reactivity. There are significant associations between both groups and substance abuse problems. Externalizing is associated with less control. Psychopathic individuals are able to exercise control, but they are oblivious to context and cues. Even if individuals with psychopathy have less severe addiction, it seems the problems that result from their addiction are more severe because they do not learn from previous serious consequences for disinhibitory behavior. In short, the relationship between the two groups and addiction is different, but can be equally severe in terms of outcomes.

Delay Discounting and the Development of Interventions to Treat Substance Abuse

Warren Bickel, PhD, Virginia Tech Carilion Research Institute

Addiction is robust and relatively insensitive to efforts to induce change. The best and most frequently used interventions often produce modest results. A new theoretical framework and empirical findings can lead to a new approach to treatment development.

New Addiction Theory

The temporal horizon for heroin addicts versus non-addicted controls is considerably shorter. When asked what they thought about their future, heroin addicts referred to their future as an average of the next 9 days compared to 4.7 years reported by participants in the control group. Addicts value the time course of positive and negative outcomes differently; they tend to care less about what happens in the future and focus more on the short term. Delay discounting can be used to accurately explore this phenomenon.

Delay discounting refers to the reduction in value of a reinforcer as a function of the delay to reinforcer delivery. The psychophysical titration procedure was developed through basic research with pigeons and was later used with humans.¹¹ The adjusting procedure begins with options far apart and then moves them closer. The results of this experiment using heroin addicts indicate a 10-fold difference in delay discounting between addicts and controls.¹²

Delay discounting is a multi-component process. When individuals make choices that favor the immediate option, there is greater activation in the ventral striatum, medial orbitofrontal cortex, and medial prefrontal cortex. Future-oriented choices were associated with greater activation in the prefrontal cortices.¹³ These findings led to the development of a new addiction theory based on the competing brain regions hypothesis.¹⁴ The addiction theory delineates the impulsive and the executive systems. The impulsive system is embodied in the amygdala, nucleus accumbens, ventral pallidum, and related structures and functions as a biological reinforce (hyperactive). The executive system is embodied in the prefrontal cortex, and its functions include valuing the future, planning, and remembering recent events (hypoactive).

¹¹ Mazur, J. (1987). An adjusting procedure for studying delayed reinforcement. In M. L. Commons, J. Mazur, J. A. Nevin, & H. Rachlin (Eds.), *Quantitative Analyses of Behavior V: The Effect of Delay and of Intervening Events on Reinforcement Value* (pp. 55-73). Hillsdale, NJ: Erlbaum.

Rachlin, H., Raineri, A., & Cross, D. (1991). Subjective probability and delay. *Journal of the Experimental Analysis of Behavior*, 55, 233-244.

¹² Madden, G. J., Petry, N. M., Badger, G. J., & Bickel, W. K. (1997). Impulsive and self-control choices in opioid-dependent patients and non-drug-using control participants: Drug and monetary rewards. *Experimental and Clinical Psychopharmacology*, 5, 256-262.

¹³ McClure, S. M., Laibson, D. L., Lowenstein, G., & Cohen, J. D. (2004). Separate neural systems value immediate and delayed monetary rewards. *Science*, 306, 503-507.

¹⁴ Bickel, W. K., Miller, M. L., Yi, R., Kowal, B. P., Lindquist, D. M., & Pitcock, J. A. (2007). Behavioral and neuroeconomics of drug addiction: Competing neural systems and temporal discounting processes. *Drug and Alcohol Dependence*, 90, S85-S91.

Many studies have contributed to knowledge about how greater discounting is associated with a wide range of behaviors including substance addiction, problem gambling, obesity, risky sexual behavior, preventive health behaviors, debt, and outcomes in clinical trials of behavior change.

Intervention Development

The new addiction theory, rooted in behavioral and neuroeconomic basic science, suggests addiction as a dimensional construct. People can vary on their levels of impulsive versus executive decision systems. For example, a person from low socioeconomic background may have had to constantly worry about staying safe and getting basic needs met and therefore may not have developed as adequate an executive system. Alternatively, a person could have a very high-level executive decision system as well as a high-level impulsive system. This dimensional construct and the variations that result have implications for treatment design. Interventions could either boost the executive system, inhibit the impulsive system, or both, depending on the individual.

Dr. Bickel and his colleagues have worked to develop and test an executive function therapy.¹⁵ Stimulant addicts completed a variety of assessments (e.g., discounting, go–no go) and then were randomized to treatment or control conditions. The active treatment consisted of four computerized memory rehabilitation modules involving sequential recall and verbal memory tasks. Treatment group participants received reinforcement for correct answers. The control group participants received the same treatment, but were provided the correct answers. Participants in the treatment group were more likely to have decreased discount rates after the intervention than those in the control group. The team has conducted systematic replications with smokers and alcoholics and found similar results.

The competing neurobehavioral decision system model provides a new theoretical framework to explain addiction. The framework suggests that treatment should target executive dysfunction. Dr. Bickel's earlier work suggests that executive function therapy can remediate deficiencies in the valuation of the future.

Question and Answer

There are a variety of ways to provide reinforcement, and delayed discounting is one element that should be considered. Addicts need to be treated as they are, not as we want them to be. If they currently value rewards over short durations, then frequent, small rewards will be more effective than delayed larger rewards. Personalized treatment incorporates the individual's discount rate into the incentive structure. Greater future discounting predicts poor treatment

¹⁵ Bickel, W. K., Yi, R., Landes, R. D., Hill, P. F., & Baxter, C. (2011). Remember the future: Working memory training decreases delay discounting among stimulant addicts. *Biological Psychiatry*, 69, 260-265.

outcomes so delaying feedback, even if it is a greater reward, will not likely be effective for addicts controlled by immediate events.

There may be as many as three processes within delayed discounting: anticipating the reward, strength of reaction to immediate incentives, and cognitive control. An intervention that focuses on general executive function may or may not address all of these processes.

There are parallels between this work and research on sleep. Individuals who are not well rested exhibit poor executive function during the day, which leads to more impulsive decision-making. Literature on sleep deprivation and discounting has yielded heterogeneous outcomes that depend on participants (e.g., medical students versus a cross-section of individuals).

A person's general discounting rate appears to be consistent across items, although the magnitude and the specifics of the reinforcer have some effect; that is, a single apparatus may be used to make the evaluations, and the evaluations are applied in the same way to multiple commodities. Discounting is a trans-disease process that operates in multiple disorders, particularly when there is dysregulation of dual systems. The unique characteristic of hyperbolic discounting is that it permits and specifies dynamic changes in choice. When people are asked to make a choice about future preferences (e.g., dessert) they say they are not interested. However, when an opportunity is presented to them (e.g., dessert cart appears), preferences can reverse on the spot.

Dynamic changes of discount rates within subjects need further study. Repeating discounting tasks produces results that are stable up to 1 year, but it has been shown that discount rates can be changed. A recent study by Dr. Bickel examined changes in discounting among heroin addicts who received medication and cognitive behavioral therapy (CBT). The next step is to determine exactly what treatment components are needed to change a person's discount rate.

Empirically Grounded Treatment Generation for Insomnia, Bipolar Disorder, and Depression

Allison Harvey, PhD, University of California, Berkeley

Dr. Harvey presented three examples of the treatment generation process being directly informed by basic science. Throughout the presentation, she referred to the NIH research stage model in which Stage 0 refers to basic science, Stage 1 refers to treatment generation, and Stage 2 refers to efficacy research.

Cognitive Model of Insomnia and Implications for Treatment Development

CBT for insomnia (CBT-I) is a multi-component treatment that has been shown to be effective in multiple meta-analyses and a review by the Standards of Practice Committee of the American

Academy of Sleep Medicine.¹⁶ CBT-I includes several components: stimulus control, sleep hygiene, sleep restriction, relaxation training, paradoxical intention, and targeting unhelpful beliefs about sleep. However, 20 to 30 percent of patients achieve full remission with CBT-I, and 19 to 26 percent are treatment resistant. The overall average improvement is 50-60 percent, yet many patients continue to experience residual sleep disturbances. CBT-I can yield a degree of change that is likely to be clinically significant but not enough to convincingly move the average patient into "good sleeper" range. Total sleep time is typically improved by an average of only 30 minutes with CBT-I.

Multiple levels of explanation contribute to multiple causal chains for insomnia including cognition, biology, social, environment/culture/family context, personality, behavior, and emotion. Although there is almost no research on the mechanisms of change, CBT-I is thought to mainly target the behavioral level of explanation.

On the basis that exploring which other levels of explanation can be leveraged to bring about improvements in treatment outcome, Dr. Harvey and colleagues probed insomnia at the cognitive level of explanation.¹⁷ The first phase of treatment development was to devise a conceptual model of the role of cognitive processes in insomnia, derived from existing Stage 0 empirical research. Second, a series of experimental manipulations were conducted to test and refine the model.

Third, a series of treatment experiments were conducted to check if reversing the cognitive maintaining processes specified in the conceptual framework improved symptoms (Stage 0/1). Fourth, the treatment developed via this scientific process was tested. The primary outcome measure in this open trial of cognitive therapy (CT) for insomnia (n = 19) was the insomnia severity index. The pre- and post-treatment drop improvement on this measure was maintained at 12 months. The same pattern was found in the targeted process measures of beliefs, safety behaviors, attention bias for sleep-related threat, and worry/rumination about sleep (Stage 1).

Moving to Stage 2 of the NIH Model of Treatment Development, the next step was to compare the newly developed treatment with existing treatments. A two-site study comparing behavioral, cognitive, and cognitive behavioral therapies was conducted with 188 randomized participants. All three treatments yielded similar benefit as measured by reduction in insomnia severity score post-treatment. At 6 months, response and remission rates indicate that CBT is more effective than the individual components of behavioral therapy (BT) and CT. The potential for Stage 2 research to feedback into Stage 0 research is demonstrated by the finding that there was a short-term advantage for BT over CT and a longer-term advantage for CT over BT. This

¹⁶ Morin, C. M., Bootzin, R. R., Buysse, D. J., Edinger, J. D., Espie, C. A., & Lichstein, K. L. (2006). Psychological and behavioral treatment of insomnia: An update of recent evidence (1998-2004). *Sleep, 29*, 1396-1406.

¹⁷ Harvey, A. G. (2002). A cognitive model of insomnia. *Behaviour Research and Therapy, 40*, 869-893.

provides a fascinating window into the process of behavior change and will likely result in the research team going back to Stage 0 research to understand the results.

Bipolar Disorder and Sleep

Another example of basic research informing Stage 1 treatment development research is in bipolar disorder and sleep. A plethora of Stage 0 research indicates the importance of sleep in bipolar disorder. Sleep symptoms are among the most prominent correlates of episodes and inadequate recovery. The evidence is accumulating that sleep disturbance is pervasive in individuals with bipolar disorder and is not just epiphenomenal to other processes but is potentially very significant. Sleep disturbance is the most common prodrome of mania and the sixth most common prodrome of depression. Sleep loss is highly correlated with daily mood symptoms, and induced sleep deprivation triggers hypomania or mania in some patients.

Dr. Harvey and colleagues have just completed a small pilot RCT to discover if insomnia is a pathway contributing to the provocation and/or maintenance of symptoms and impairment in bipolar disorder by comparing sleep treatment (CBT-I for bipolar) and psychoeducation. Both treatments yielded improvement in insomnia severity index scores, but multilevel models showed the rate of change in the CBT-I group was greater relative to the psychoeducation group. The psychoeducation group also was more than eight times as likely to relapse from the start of treatment through the 6-month follow-up relative to the CBT-I group. These preliminary results should be interpreted with caution given the small sample size (n = 52, 77 percent retention at 6 months).

Memory Impairment

There are some intriguing findings in the literature concerning memory impairment. Patients forget one-third of the contents of treatment sessions, and for some types of recommendations, recall is as low as 13 percent. Memory impairment is characteristic of mental illnesses such as bipolar disorder, schizophrenia, post-traumatic stress disorder, anxiety disorders, and major depressive disorder. It could be critical that memory impairment, which is prevalent in many mental health disorders, be taken into account when designing interventions. Patients cannot implement treatment recommendations if they cannot remember them.

The broad goal is to develop a simple and inexpensive intervention for memory impairment that can be used across multiple disorders and multiple treatments, particularly psychosocial treatments given that they are typically delivered at 50-minute weekly sessions and memory for these sessions is poor. Dr. Harvey and colleagues are currently reviewing literature for principles of memory and cognitive support methods, building cognitive support into CT for depression, and designing treatment experiments to identify the most powerful cognitive support techniques (Stage 0). A pilot RCT is scheduled to begin in January 2013 that will compare CT for depression as usual with CT plus the memory-enhancing intervention (Stage 1).

The hypothesis is that patients receiving the memory-enhancing intervention will have better outcomes.

In summary, several interventions are effective for various disorders, but there is still room for improvement. Basic research (Stage 0) and short inexpensive treatment experiments have great potential to fuel intervention generation and refinement. Treatment experiments are used to test and optimize specific strategies to reverse maintaining processes. It was argued that treatment experiments are an important and underutilized opportunity to ensure that specific treatment procedures are effective prior to adding them to a multi-component treatment. Also, Dr. Harvey demonstrated how research in Stages 0-2 can be reciprocal, iterative, recursive, and creative.

Question and Answer

As part of the experiment on memory impairment, the team is coding therapist tapes and treatment manuals for cognitive support to clearly explicate what is done during CBT in terms of cognitive support. The focus is what happens during a session. The goal is not to remind patients to do their homework; it is to remind them to remember their sessions.

Open Discussion

Moderator: Timothy Strauman, PhD, Duke University

Dr. Strauman identified three levels of intervention research: (1) macro studies of effectiveness using large datasets, multiple populations, and multiple interventions; (2) meso studies of traditional efficacy and effectiveness of single interventions; and (3) micro experimental studies of specific techniques or hypothesized mechanisms.

Micro-intervention studies represent a type of research where theory and mechanism intersect with effectiveness and implementation. Specification of mechanism and technique, typically based on a theoretical framework, is required. Micro studies allow for immediate assessment of impact in a way that provides feedback to the basic researcher. Micro studies draw together people who care about theory and people who care about the field. It was posited that basic scientists must tailor their experiments into interventions intended to bring about change on some clinically relevant dimension. Implementation scientists must temporarily suspend their assumptions about the context in which interventions are delivered. New partnerships between basic and intervention researchers are important. The four presentations in the first panel are outstanding exemplars of this type of research.

The first three presentations described research that takes an inductive approach by starting with basic science findings, developing a model, and evaluating it in a clinical setting (Amir, Newman, and Bickel). The fourth presentation provided a different approach of dismantling an existing, generally effective intervention consisting of multiple components to determine which components are the active ingredients (Harvey). Several participants discussed when each of these approaches might be appropriate. Smaller studies of specific basic science findings allow

researchers to refine possible interventions. Dismantling studies may be effective for clinical care. The approach depends on the problem and the theory. In some areas, decent treatments are already available (e.g., CBT-I), but how they work and for whom they work is not fully understood; these are appropriate for dismantling approaches. Other areas, where the literature is inconsistent (e.g., child depression and anxiety) or where there is treatment resistance (e.g., disinhibiting behaviors in the prison population), are good targets for novel treatment development and delivery.

Incorporating Use-Inspired Basic Research into Research on Intervention Efficacy

Mechanism of Change in the Treatment of Depression

Robert DeRubeis, PhD, University of Pennsylvania

A common design in treatment research is to examine both a mediator and outcome over time from pre- to post-treatment. Another common design is to measure change in the mediator over the initial phase of treatment and correlate it with outcome over time. However, these designs do not rule out reverse causality or that the mediator is just another measure of symptoms. It is difficult to get the temporal order correct. Ideally, the mediator would be measured at two points and outcomes measured subsequently, but it is unclear how much time should pass between measuring the mediator before it produces an effect on outcome and measuring the outcome. In most theoretical frameworks, the interval is very short. Key questions include: when is the best time to catch the interval, and is it the same for all (or most) subjects?

A typical research design for examining therapeutic alliance¹⁸ (i.e., the collaborative aspect of the relationship between therapist and clients in the context of psychotherapy) is that the alliance is measured at some point during the course of the treatment. If alliance is correlated between pre- and post-treatment, then it is tempting to infer early alliance predicts overall outcome. However, this design does not rule out reverse causality: early outcome predicts later alliance. Several studies using an approach that can rule out reverse causality yield a mixture of mostly positive, but weak, findings (mean weighted $r = 0.11$). Estimates in the literature from research that fails to account for the temporal order of the assessments tend to be higher than this (ranging from $r = .25$ to $.30$).

There are two primary factors of the therapeutic alliance in cognitive therapy: (1) agreement, but not relationship, predicts subsequent symptom change and (2) symptom change from beginning to end of treatment predicts agreement and relationship. The latter is not what is typically thought. One alternative to capturing the temporal sequence would be to isolate the

¹⁸ Bordin, E. S. (1979). *The generalizability of the psychoanalytic concept of the working alliance*. *Psychotherapy: Theory, Research, and Practice*, 16, 252-260.

variables in the laboratory, which is more difficult to do in implementation studies. A second alternative is to study change points early and often using mixed models. Studying change points early and often could involve repeated session-to-session change measures that would yield an overall estimate of the effect of change on the symptoms. One study using a mixed methods analysis yielded significant effect sizes for cognitive methods ($r = 0.44$) and negotiating/structuring ($r = 0.38$) and a non-significant effect size for working alliance ($r = 0.15$).¹⁹

A third alternative is to study change idiographically by locating maximum shifts in mechanisms of processes (i.e., critical incidents) or each patient's maximum inflection in outcome trajectory (i.e., sudden gains). The group mean time course of symptom change during cognitive therapy for depression shows an initial improvement and then a smooth progression of improvement. The group mean masks the heterogeneity of the patients, however, and includes non-responders (~30 percent), gradual responders (~40 percent), and responders with sudden gains (~40 percent).

Sudden gains are characterized by a large magnitude of reduction of depressive symptoms (greater than or equal to 7 points on the Beck Depression Inventory (BDI)) and high percentage change (greater than or equal to 25 percent as measured by the BDI). The gains can be tested to ensure it is a stable shift rather than an anomaly followed by a decline. Sudden gains are important because cognitive changes predict sudden gains, the improvement seen in patients with sudden gains lasts longer than others, and sudden gains predict—but are not predicted by—the therapeutic alliance. Cognitive therapy skills and the use of cognitive therapy skills predict sustained response after termination of cognitive therapy; this can indicate when a person is ready to leave therapy. In Dr. DeRubeis' study, responders who experienced sudden gains continued to score lower on the BDI than responders who did not experience sudden gains 18 months after treatment ended (significant differences at 6 and 18 months).

It is important to assess therapy processes to facilitate dissemination with high fidelity, adherence, and competence. Therapeutic alliance, especially agreement on tasks and goals, is also an important process to assess. It is difficult to test for mediation of symptom change, but it can be done with mixed models to identify sudden gains. Mediation of relapse prevention is especially important.

Question and Answer

Dr. DeRubeis' studies were not initially set up to examine sudden gains; they were discovered retrospectively. There are limited data available to connect the sudden gains to factors in the environment or relationship. An interview will be included in future studies to assess functional relationships with the sudden gains (e.g., what happened in your life at this point). It appears

¹⁹ Strunk, D. R., Brotman, M. A., & DeRubeis, R. J. (2010). The process of change in cognitive therapy for depression predictors of early inter-session symptom gains. *Behaviour Research and Therapy*, *48*, 599-606.

the sudden gains represent an “ah ha” moment or a point at which things “clicked” for the patient.

While there is some cognitive insight that comes with a sudden gain, there probably is an emotionally positive uplift effect as well that serves to consolidate the situation. When the sudden gain occurs, the therapeutic alliance is strengthened. The patient feels positively about the therapist and therapy. There is an opportunity to build upon a sudden gain session in subsequent sessions.

Sudden gains are observed during CBT for a variety of disorders in addition to depression. It is unclear to what extent this is an effect attributable to CBT in particular. The length of treatment seems to be a key factor, and it is possible that sudden gains would be seen in other interventions lasting a long time.

Understanding the Mechanisms of Action in Prolonged Exposure in the Treatment of Anxiety Disorders: The Case of PTSD

Edna Foa, PhD, University of Pennsylvania

Historically, contiguity of time was viewed as the mechanism of fear acquisition and extinction. The idea was that fear acquisition occurs when an unconditioned stimulus is repeatedly presented with a conditioned stimulus (the feared situation), and fear extinction occurs when the conditioned stimulus is repeatedly presented without the unconditioned stimulus. Because anxiety disorders were conceptualized as unrealistic fears, early exposure therapy proponents viewed the presentation of the fear situations during exposure as not containing the presentation of the unconditioned stimulus. These early proponents did not explicitly discuss mechanisms underlying exposure therapy. It can be inferred that the contiguity of time principle was assumed to explain fear reduction following therapy. However, many observations are inconsistent with the theory of contiguity of time as the mechanism of change during extinction and exposure therapy. Consequently, contemporary learning theorists posit that change in expectancy or change in the meaning of the conditioned stimulus is the mechanism of acquisition and extinction.

Another view that continues to dominate the field despite conceptual problems is that habituation is the mechanism underlying exposure therapy. In the laboratory, extinction refers to the reduction of the conditioned response as a function of the absence of the unconditioned stimulus. Habituation refers to the reduction of unconditioned response (i.e., anxiety, fear) as a function of repetitions of unconditioned stimuli; in other words, clinical theorists used the term habituation to refer to the observation that fear reduction occurs following repeated exposures to the feared stimuli. At the same time, habituation was also used to denote the mechanism that mediates fear reduction, leading to conceptual circularity between the mechanism and the empirical observation of fear reduction. The modern learning theory conceptualization of the extinction as involving a cognitive change has been ignored in this argument.

Emotional Processing Theory

Emotional processing theory (EPT) was developed to provide a conceptual framework for understanding the anxiety disorders and the mechanisms involved in their treatment that integrates current knowledge of conditioning and extinction with information processing theories.²⁰ The starting concept in EPT is the notion that fear (or other emotions) is represented as a cognitive structure that includes information about the feared (emotional) stimuli, the fear (emotional) responses, and the meaning of these stimuli and responses. Pathological fear structures included unrealistic (pathological) associations among the representations as well as erroneous evaluations of the meaning associated with the stimuli and responses elements (anxiety persists until escape occurs or erroneous estimates of danger). Each anxiety disorder is characterized by specific pathological elements.

Within the framework of EPT for post-traumatic stress disorder (PTSD), a trauma memory is conceptualized as a specific fear (emotional) cognitive structure. Thus, a trauma memory includes stimuli present during the trauma, physiological and behavioral responses that occurred during the trauma, and meanings associated with these stimuli and responses. Dysfunctional, negative beliefs that underlie PTSD (e.g., the victim is incompetent and untrustworthy, no place is safe) is embedded in associations among stimulus, response, and meaning representations that are unrealistic and therefore, pathological.

The goal of exposure therapy for PTSD (as well as for other anxiety disorders) is to reduce symptoms via correction of the pathological elements in the trauma memory or via forming a new trauma memory that accurately represents reality and competes with the original trauma memory. Exposure therapy aims to achieve this goal via repeated revisiting of the traumatic memory via imaginal exposure to process the experience. Repeated in vivo exposure to situations the patients avoid because of trauma-related fear are also used. Emotional processing is the mechanism by which a new, non-pathological structure is formed. Two conditions must be met for exposure therapy to successfully correct the emotional structure underlying each anxiety disorder: during exposure, the fear (emotional) structure must be activated (emotional engagement), and the information that is incompatible with the pathological elements in the patient's pathological structure needs to be available (e.g., change in expectancy). Indicators of emotional processing include fear activation, which is also a mechanism, and habituation (fear reduction) within and between sessions. Early emotional processing theory hypothesized that these indicators would be related to successful treatment, although habituation was not viewed as a mechanism.

²⁰ Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: Exposure to corrective information. *Psychological Bulletin*, 99, 20-35.

Evidence suggests there is a relationship between fear activation and treatment outcome. Imaging studies have shown that amygdala activation is present during extinction²¹ and that greater amygdala activity during extinction predicts greater degree of extinguished fear.²² Fear activation is correlated with treatment outcome, and these data support the hypothesis that fear activation is a fundamental mechanism of exposure therapy.

Studies have examined the relationship within and between session habituation and treatment outcomes. For example, a study comparing 60-minute versus 30-minute imaginal exposure for PTSD patients found that habituation within sessions was unrelated to outcome.²³ The implication is the length of exposure therapy sessions can be reduced, which will aid in dissemination of the intervention. Another study by Dr. Foa and colleagues (in preparation) has found that as hypothesized by EPT, reductions in trauma-related negative cognitions was a causal factor in improvements in PTSD and depression over the course of prolonged exposure.

Conclusion

EPT delineates the mechanisms involved in anxiety disorders (e.g., pathological fear (emotional structures) and the mechanisms involved in treatment of these disorders (e.g., fear activation and disconfirmation of pathological associations). There is strong evidence for a positive relationship between fear activation and treatment outcome emerging from both animal experiments and human studies. There is no support for a relationship between within-session habituation (fear reduction) and outcome. The relationship concerning between-session habituation and outcome is equivocal and requires further study. Results have been inconsistent with the view that habituation is the mechanism of symptom reduction in exposure therapy. Studies support the hypothesis of EPT that the two mechanisms involved in exposure therapy are fear activation and the reduction of negative cognitions (change in expectancy).

Where Mind Meets Matter: A Translational Approach for Treating Anxiety Disorders

Stefan G. Hofmann, PhD, Boston University

A meta-analysis of RCTs comparing CBT and placebo interventions for a variety of anxiety disorders including acute stress disorder, OCD, PTSD, social anxiety disorder, generalized anxiety disorder, and panic disorder yielded generally positive outcomes for reduction of anxiety and depression outcomes.²⁴ However, it is clear there is room for improvement, and

²¹ LaBar, K.S., Gatenby, J.C., Gore, J.C., LeDoux, J.E., and Phelps, E.A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. *Neuron*, 20, 937-945.

²² Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, 43, 897-905.

²³ Van Minnen, A., & Foa, E. B. (2006). The effect of imaginal exposure length on the outcome of treatment for PTSD. *Journal of Traumatic Stress*, 19, 427-438.

²⁴ Hofmann, S. G., & Smits, J. A., (2008). Cognitive behavioral therapy for adult anxiety disorders: A meta-analysis of randomized controlled trials. *Journal of Clinical Psychiatry*, 69, 621-632.

the results raise questions of specificity because some disorders were more responsive than others. Similar mixed results are apparent for meta studies of serotonin-specific reuptake inhibitor (SSRI) treatments and combination therapies. It is unclear why combination therapy does not provide a consistent clear advantage.

Augmentation of Exposure Therapy with D-Cycloserine

While exposure therapy is one of the most effective interventions for particular anxiety disorders, it is possible that its effects could be enhanced or augmented at the molecular level of learning. Antagonists at the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor block fear learning and extinction. D-Cycloserine (DCS), an antibiotic shown to be safe in humans, is a partial agonist at the NMDA receptor that appears to augment learning and facilitate extinction of conditioned fear in small doses at the time of treatment.²⁵

Ressler et al. demonstrated that exposure therapy for patients with fear of heights who received a single dose of DCS prior to treatment maintained significantly larger reductions of phobia and anxiety symptoms.²⁶ The results were maintained at 3 months. This successful pilot study led to additional studies with patients with social anxiety disorder, OCD, and panic disorder, all of which replicated the positive results, although the OCD trial showed a diminishing effect of DCS over time.²⁷

In general, the collection of studies has found that DCS augments or speeds up CBT for anxiety disorders 25 percent faster than the placebo.²⁸ Further research is needed to better determine (1) predictors of treatment response; (2) for which disorders DCS is most effective (i.e., found opposite effect with PTSD patients, possibly because the medication augments reconsolidation

²⁵ Hofmann, S. G., Meuret, A. E., Smits, J. A., Simon, N. M., Pollack, M. H., & Eisenmenger, K. et al. (2006). Augmentation of exposure therapy with D-Cycloserine for social anxiety disorder. *Archives of General Psychiatry*, *63*, 298-304.

²⁶ Ressler, K. J., Rothbaum, B. O., Tannenbaum, L., Anderson, P., Graap, K., Zimand, E. et al. (2004). Cognitive enhancers as adjuncts to psychotherapy: Use of D-Cycloserine in phobic individuals to facilitate extinction of fear. *Archives of General Psychiatry*, *61*, 1136-1144.

²⁷ Guastella, A. J., Richardson, R., Lovibon, P. F., Rapee, R. M., Gaston, J. E., Mitchell, P. et al. (2008). A randomized controlled trial of D-Cycloserine enhancement of exposure therapy for social anxiety disorder. *Biological Psychiatry*, *63*, 544-549.

Hofmann et al. (2006).

Otto, M. W., Tolin, D. F., Simon, N. M., Pearlson, G. D., Basden, S., Meunier, S. A. et al. (2010). Efficacy of D-Cycloserine for enhancing response to cognitive behavior therapy for panic disorder. *Biological Psychiatry*, *67*, 365-370.

Wilhelm, S., Buhlmann, U., Tolin, D. F., Meunier, S. A., Pearlson, G. D., Reese, H. E. et al. (2008). Augmentation of behavioral therapy with D-Cycloserine for obsessive-compulsive disorder. *American Journal of Psychiatry*, *165*, 335-341.

²⁸ Hofmann, S. G., Smits, A. J., Rosenfield, D., Simon, N., Otto, M. W., Meuret, A. E. et al. (In press). D-cycloserine as an augmentation strategy of cognitive behavioral therapy for social anxiety disorder. *American Journal of Psychiatry*.

of the activated fear structure before extinction); and (3) the optimal dose of both CBT and DCS.

Biological Predictors of Treatment Response

There are no known behavioral or biological predictors of CBT treatment response for patients with social anxiety disorder. Doehrmann et al. recently examined neuroimaging-based treatment prediction.²⁹ Participants received CBT and exposure therapy in weekly 2.5-hour small group sessions for 12 weeks. Initial severity of social anxiety predicted treatment response quite well and therefore was used as a covariate in the analysis. The treatment resulted in a 79 percent response rate.

The researchers conducted a number of experiments using functional magnetic resonance imaging (fMRI) to examine predictors. They found that LSAS change was associated with activation in the dorsal occipital and ventral occipital clusters. The results indicate that fMRI at pre-test can predict 40 percent of the variance in CBT response, above and beyond the benchmark prediction offered by initial disorder severity.

Question and Answer

It was noted that the success of DCS is somewhat inconsistent in the literature depending on dose, duration, and the particular anxiety disorder being treated. Dr. Hofmann has found that a small dose of 50-150 milligrams 1 hour prior to no more than four weekly sessions in a row appears to be the most effective. The results have been largely positive for OCD, panic disorder, and social anxiety disorder. PTSD, especially combat-related PTSD, is a more complex disorder, and results are dependent on the quality of the trauma exposure therapy. Further research is needed on DCS and PTSD in order to better examine the mechanism and the most effective exposure practices. There is evidence to suggest that DCS not only augments extinction learning, but also can augment reconsolidation of fear memory. Therefore, DCS can make a good exposure better and a bad exposure worse.

Doehrmann et al. did structural scans as well (only fMRI data were published), which indicated stronger connectivity of the amygdala to the prefrontal cortex predicted better treatment effects.

²⁹ Doehrmann, O., Ghosh, S. S., Polli, F. E., Reynolds, G. O., Horn, F., Keshavan, A. et al. (2012). Predicting treatment response in social anxiety disorder from functional magnetic resonance imaging. *Archives of General Psychiatry*, doi:10.1001/2013.jamapsychiatry.5.

Open Discussion

Moderator: Richard Bootzin, PhD, University of Arizona

Research on Mechanisms

Mechanisms tend to be neglected in efficacy research. Participants discussed whether and when it might be useful and interesting to study mechanisms in cases where there is no effect from the treatment (or placebo). The mechanisms at work during behavior change are likely different from mechanisms of maintenance of behavior change. Dr. DeRubeis' presentation illustrated that examining mechanisms is a good way of testing what are often used as alternative hypotheses (e.g., therapeutic alliance).

Non Self-Report Measures

Participants noted that it was refreshing to see several examples of non self-report measures such as facial expression and neuroimaging. While self-report measures can be useful, it is important not to rely on them exclusively. Biological measures should be incorporated into this type of research, when applicable.

Length of Treatment

CBT and other cognitive therapies are all complicated treatments, and consistent dissemination is a challenge. The ideal length of treatment for patients is not always known. In research design, the number of sessions is often determined a priori. One goal of research is to determine how few sessions are necessary to obtain a decent outcome, while also paying attention to long-term effects and maintenance of behavior change.

Heterogeneity of Treatment Response

Heterogeneity of treatment response has implications for intervention efficacy. A large portion of the depressed population is likely not severely depressed and may respond to any treatment. Others who are treatment resistant will require greater attention to treatment fidelity and length of treatment. It is possible that treatments could be tailored to individual profiles in the future, which would require exploration of the treatment features that can be altered. Genetic markers, once identified, could be used to identify people who will likely have poor treatment response.

Explicitly studying heterogeneity of treatment response requires studies with sufficient statistical power to identify different patterns of response. Researchers do not necessarily have to be limited by the DSM-IV diagnosis categories. The National Institute of Mental Health (NIMH), for example, is encouraging applications that look at mechanisms without being constrained by the DSM-IV categories. There are likely more meaningful ways to group people that would allow for the optimization of treatment response.

Neurotrophic Pathways

The beauty of DCS is that it is very clear how it works on a molecular level; the location and neurotrophic pathway are known. Other agents are possible moderators (e.g., cortisol, oxytocin), but they are more complex and it is difficult to know exactly what pathway is involved.

Sudden Gains

Participants noted that the work on sudden gains is fascinating. It is unknown exactly what a treatment might look like if eliciting a sudden gain was an explicit outcome goal. Patients tend to respond well when they are engaged, involved, and asked to produce ideas through the Socratic method. Patients might have a sudden gain when they review specific events and realize another way of conceptualizing what happened.

Expanding Methods for Testing Mechanisms of Action

Experimental Designs for Intervention Development

Inbal Nahum-Shani, PhD, University of Michigan

Many behavioral interventions contain multiple components; a component refers to any piece of an intervention that can be reasonably separated out for study purposes. Typical components include the content, intervention modality, features to promote adherence or compliance, and features to improve fidelity.

An example of a multi-component intervention is Project Quit, a web-based smoking cessation intervention. This intervention includes multiple components such as a success story, outcome expectation, efficacy expectation, and personalized source. In many cases investigators would take an "evaluation" approach to intervention development, typically using four steps: (1) establish a theoretical model; (2) identify a set of intervention components; (3) form an intervention version out of the components; and (4) confirm the effectiveness of the intervention with an RCT. However, this approach does not enable the investigators to address critical questions concerning (a) the efficacy of individual intervention components (e.g., to identify which of the components are effective, which level of each component is effective, and which components work well together and which do not) and (b) the optimal sequencing and tailoring of intervention components (e.g., which component should be offered first, which component should be offered subsequently, and how intervention components should be tailored over time in response to the specific and changing needs of the participant). These questions are critical to answer in order to develop an effective, high-quality version of the intervention, before comparing the intervention to a control.

Two alternative experimental designs can address the critical questions noted above. Factorial designs can be used to screen out the intervention components and address questions

concerning the efficacy of individual components of an intervention. Sequential, multiple assignment, randomized trials (SMART) are useful for answering questions concerning the optimal way to sequence intervention components over time and adapt the intervention components to the changing needs of the participant.

Factorial Design

Factorial designs typically involve more than one factor. Different levels of each factor are crossed with the levels of the other factors. For example, to screen out two components of the Project Quit intervention (e.g., success story and the personalized source) we consider two factors (e.g., one for success story and one for personalized source), each with two levels (on/off). These two factors can be crossed to form a 2x2 factorial design that will enable the investigator to determine if each of the components should be included in the intervention or not. This can be done by testing the main effect of each factor. Assume that we add a third factor, aiming to test whether a third component should be included in the intervention or not (e.g., to test whether or not we should include a message concerning efficacy expectations in the intervention). A 2x2x2 factorial design can be used to screen out all three components. Given a specific sample size, effect size, and alpha level, adding another factor to be tested (i.e., screening three intervention components instead of two) will not result in reduced power for detecting main effects. Factorial designs are useful for screening experiments in which the primary aims concern testing main effects, rather than the comparison of individual experimental conditions.³⁰

SMART Design

SMART designs were specifically developed to help investigators construct adaptive interventions based on empirical evidence. SMART designs are randomized trials that include multiple stages of randomizations, with each stage corresponding to a critical decision/scientific question concerning the sequencing or tailoring of intervention components over time. For example, in a study of adaptive interventions for children with ADHD the investigators used a SMART design to address two primary questions: (1) should medication or behavioral intervention be given first and (2) should non-responders be given an increased dose or should we augment the initial treatment with the alternate.³¹ Data from SMART designs can inform the development of a high-quality adaptive intervention before it is compared to a control. This design can be used for comparing intervention options at each stage, comparing embedded adaptive interventions, and for more deeply tailoring adaptive interventions.³²

³⁰ Dziak, J., Nahum-Shani, I., & Collins, L. M. (2012). Multilevel factorial experiments for developing behavioral interventions: Power, sample size, and resource considerations. *Psychological Methods, 17*, 153-175. See also <http://methodology.psu.edu/ra/most/factorial>.

³¹ Nahum-Shani, I. Qian, M., Almirall, D., Pelham, W. E., Gnagy, B., Fabiano, G. A. et al. (2012, October). Experimental design and primary data analysis methods for comparing adaptive interventions. *Psychological Methods*, doi: 10.1037/a0029372.

³² Murphy, S. A. (2005). An experimental design for the development of adaptive treatment strategies. *Statistics in Medicine, 24*, 1455-1481.

Question and Answer

In SMART designs mediators of the effect of the initial intervention can also be moderators (or even potential tailoring variables) for the second-stage intervention. It is possible, for example, that the behavior intervention might be more burdensome to the family than medication, thereby reducing family satisfaction. Family satisfaction might be a mediator because it drives response and possibly primary outcomes. Family satisfaction from initial intervention might also be a moderator of the second-stage intervention options, because if the family is not satisfied with the treatment, then it might be better to offer them the alternative treatment rather than to intensify the same intervention. Baseline and intermediate outcomes variables collected in the course of a SMART can be used to further tailor intervention components.

SMART designs can be powered depending on the primary scientific questions: to detect the difference between the first-stage intervention options; to detect differences between the second-stage intervention options; and to detect differences in the embedded adaptive interventions. The design is typically powered to detect the most primary research question, driven by science.

For screening purposes, the primary aims of a factorial experiment concern the main effects of the factors, but it can also be used to test for interactions among factors to determine whether certain intervention components work well together or not.

Moderators, Mediators, and Mechanisms

David MacKinnon, PhD, Arizona State University

Understanding the differences between moderators, mechanisms, and mediators can be challenging. A moderator is a variable that affects the strength or sign of the relationship between X and Y. It is reasonable to expect that the effects of interventions may differ across individuals. A mechanism is the true underlying process by which one variable transmits its effect to another variable. Measuring mechanisms can be challenging.

A mediator is a variable that is intermediate to the causal process relating an independent to a dependent variable. Examples include (1) motivational interviewing alters client language, which affects drinking outcomes; (2) therapy reduces craving, which reduces consumption; and (3) therapy increases spirituality, which reduces alcohol consumption.³³ Mediation in behavior

See also <http://methodology.psu.edu/ra/adap-treat-strat>.

³³ Kelly, J. F., Stout, R. L., Magill, M., Tonigan, J. S., & Pagano, M. E. (2011). Spirituality in recovery: A lagged meditational analysis of Alcoholics Anonymous' principal theoretical mechanism of behavior change. *Alcoholism: Clinical and Experimental Research*, 35, 454-463.

Moyers, T. B., Martin, T., Christopher, P. J., Houck, J. M., Tonigan, J. S., & Amrhein, P. C. Client language as a mediator of motivational interviewing efficacy: Where is the evidence? *Alcoholism: Clinical and Experimental Research*, 31, 40-47.

change research is important because theoretical questions are about mediating processes. Identifying critical ingredients of interventions will lead to more efficient treatments. Studying mediation provides a scientific approach to understanding how interventions induce effects and provides an opportunity for studying many interesting statistical and mathematical issues.

Mediation Model

The Stimulus-Organism-Response (SOR) theory is a simple way to illustrate the mediation model. The stimulus and response are known, but what happens in between (mental and other processes) is less obvious. The mediation process is usually unobservable and may operate at different levels (e.g., individuals, neurons, cells, atoms, families, therapy groups, clinics, states). Multiple mediating processes may happen simultaneously and may be part of a longer chain. The researcher needs to define what part of a long mediation chain to study. Mediation is about getting a better way to measure the mechanism(s). Regression equations can be used to test mediation.³⁴

The coefficients in the equations may be obtained using ordinary least squares regression (OLS), covariance structure analysis, or logistic regression. The product of coefficients test is the method of choice; it extends to more complicated models such as the multiple mediator model. The coefficients (a and b) are assumed to have a normal distribution, but the product of coefficients will not, so it is more accurate in statistical tests. Non-normality of the product of coefficients also can be addressed by bootstrapping. There are several inferential assumptions: (1) measures are reliable and valid; (2) data are a random sample from the population of interest; (3) the coefficients reflect true causal relationships and the correct functional form; (4) the mediation chain is correct; and (5) there are no moderator effects.

Mediation analysis should be conducted even when there is no program effect in order to determine if there is conceptual theory failure or if the mediator manipulation failed. There are two types of theories of the mediated effect: conceptual theory and action theory. Conceptual theory outlines how hypothesized mediators are linked to outcomes of interest. Conceptual theory addresses whether or not the right mediators are selected and whether or not they are causally related to the dependent variable. Action theory outlines how a manipulation (X) relates to hypothesized mediators. Action theory addresses whether and how the selected mediators can be changed.

Both mediation and moderation effects are important to study because they allow the researcher to look at types of people and mediation at the same time. Mediation and moderation help investigators to understand how manipulations achieve effects and identify

Witkiewitz, K. A., Bowen, S., & Donovan, D. M. (2011). Moderating effects of a craving intervention on the relation between negative mood and heavy drinking following treatment for alcohol dependence. *Journal of Consulting and Clinical Psychology, 79*, 54-63.

³⁴MacKinnon, D. P. (2008). *Introduction to Statistical Mediation Analysis*. New York: Erlbaum.

See also <http://ripl.faculty.asu.edu/mediation/>.

characteristics of participants and/or environment that moderate effectiveness of a manipulation. Treatments can be improved by understanding for whom and under what conditions they operate. Hypotheses can be tested regarding the specificity of results across groups. Finally, studying both mediation and moderation can inform differential treatment response and enable treatments better targeted to subgroups.

Several assumptions are necessary for longitudinal mediation analysis. First, the correct temporal ordering is assumed (X before M before Y). Second, relationships among X, M, and Y are at some equilibrium, so the observed relations are not solely due to when they are measured. Finally, the correct timing and spacing of measures (i.e., when X affects M and when M affects Y) to detect effects are crucial considerations for theory and for data collection.

Causal Inference

Causal inference for mediation is an active research area.³⁵ It is assumed that there are true causal relationships and that there is a self-contained, comprehensive model for regression analysis for mediation. The problem with mediation analysis is that the mediator is not randomly assigned, but self-selected. The assumption of sequential ignorability refers to the lack of confounders influencing mediation relations in the model.³⁶ Sensitivity analysis can be conducted to determine how large a confounder effect would be needed to eliminate the mediator effect. One way to deal with omitted variable bias and improve causal inference in a mediation study is to apply statistical approaches such as (1) instrumental variable methods; (2) principal stratification; (3) inverse probability weighting; and (4) G-estimation.³⁷

There are also design approaches to improving causal inference. Statistical mediation analysis answers the question, “How does a researcher use measures of the hypothetical intervening process to increase the amount of information from a research study?” A follow-up question would be, “What is the best next study or studies to conduct after a statistical mediation analysis to test mediation theory?” The latter question can be answered with research designs to address consistency or specificity of the mediation relation.³⁸

Summary

In summary, mediation analysis is important because it provides information on how a treatment achieved its effects. Tests of mediation based on the product of the coefficients are

³⁵ See, for example, Pearl, J. (2009). *Causality* (2nd Ed.). New York: Cambridge.

³⁶ Imai, K., Keele, L., & Tingley, D. (2010). A general approach to causal mediation analysis. *Psychological Methods*, *15*, 309-334.

³⁷ G-estimation is a method of analysis based on structural nested failure time models (SNFTMs). See Robins, J. M., Blevins, D., Ritter, G., & Wulfsohn, M. (1992). G-estimation of the effect of prophylaxis therapy for pneumocystis carinii pneumonia on the survival of AIDS patients. *Epidemiology*, *3*, 319-336.

³⁸ MacKinnon, D. P., & Pirlott, A. G. (2012). *The unbearable lightness of b: Design approaches to causal interpretation of the M to Y relation*. Manuscript in preparation.

the most accurate. Models with moderation and mediation are available. Longitudinal data analyses provide an ideal way to test for mediation. Statistical methods and design approaches to address confounder bias and experimental designs to investigate mechanisms of the most effective treatments are available.

Question and Answer

Some researchers favor growth curve models because they would allow for measuring growth over time of the mediator related to outcome.

The significance of the relationships between X, M, and Y will always be the same, even if their positions change. Mediation is the theory being tested, especially with cross-sectional data.

Idiographic Functional Analysis in Treatment Development Research

David Barlow, PhD, Boston University

Anxiety and mood disorders share substantial phenotypic overlap and high comorbidity. Higher order dimensions account for almost all the covariance among DSM-IV constructs. Many thought that the DSM-5 would represent a significant advance and recognize higher order constructs but that does not appear to be the case. DSM-5 will likely further delineate small slices of diagnostic categories. At present, there are effective treatments for anxiety disorders, but with room for improvement. The existing plethora of diagnostic categories has resulted in too many distinct treatment protocols, which are too complex for any one clinician to master. This has implications for treatment dissemination.

Unified Protocol

Barlow and colleagues developed a trans-diagnostic unified treatment protocol using a modular approach.³⁹ The unified protocol is based on clinical and basic research and attempts to distill active elements of existing treatments. Core modules include emotional awareness training, cognitive appraisal and reappraisal, emotion driven behaviors and emotional avoidance, interoceptive awareness and tolerance, and situational exposures. The putative mechanism of action underlying the related disorders is the reduction of experiential emotional avoidance and the associated extinction of anxiety and distress triggered by intense emotional experiences. A series of studies have been conducted to test the equivalence of the unified protocol against protocols for treatment of individual disorders.⁴⁰

³⁹ Barlow, D. H., Farchione, T. J., Fairholme, C. P., Ellard, K. K., Boisseau, C. L., Allen, L. B., & Ehrenreich-May, J. (2011). *The unified protocol for transdiagnostic treatment of emotional disorders: Therapist guide*. New York: Oxford University Press.

⁴⁰ See, for example, Ellard, K. K., Deckersbach, T., Sylvia, L. G., Nierenberg, A. A., & Barlow, D. H. (2012). Transdiagnostic treatment of bipolar disorder and comorbid anxiety with the Unified Protocol: A clinical replication series. *Behavior Modification*, *36*, 482-508.

Idiographic Methods for Testing Mechanisms of Action

Idiographic methods for testing mechanisms of action are complementary to more typically used methods. Individual within-subject variability is not masked in a group average. Individual differences are immediately highlighted, and reasons for non-response are immediately sought, rather than waiting until the end of a trial and using unreliable retrospective reports.⁴¹

Historically, experimental psychology maintained an intense focus on individuals, which yielded major discoveries. A focus on individual differences is once again becoming increasingly popular. Group comparisons are not needed to demonstrate causal relationships. All that is needed is a controlled variation (manipulation) of the independent variable and observation of the effects on the dependent variable, which can be done using a series of individual cases (i.e., single-case experiment).

A single-case experiment involves controlled observations of the individual, systematic, and quantitative data collection, and systematic manipulation of the treatment and control conditions. This design yields rich quantitative description and allows for the study of rare phenomena, treatment/theory development, isolation of mechanisms of action, and hypothesis generation and testing. The design can also test causality, rule out alternatives, and test generality.

Two methods are involved in single-case experiments: continuous monitoring and systematic variation of treatment condition. Continuous monitoring refers to the need for frequent reading of the behavior or construct in question. Historically, it has been difficult to capture clinical behaviors with assessment. Technological advances can facilitate measurement of dynamic changes in behavior and mechanisms of change on daily, momentary, and real-time basis. Examples include daily diary cards or online reporting, momentary electronic diary studies, and real-time physiological monitoring during behaviors.

Single-case experimental design allows for systematic variation of treatment conditions to test effectiveness. The design begins with baseline assessment, and then the intervention is systematically applied, withdrawn, or modified over time within individuals. The individual serves as his or her own control. Demonstrations of changes in the independent variable leading to changes in the dependent variable suggest evidence of causality. Causal inferences are strengthened with replication of effects within subjects, within studies, and across studies. If a relationship is replicated enough within an individual while ruling out other influences on the variable, the function can be generalized across individuals. Single-case experimental designs are more feasible, efficient, and more flexible than between group designs. They allow for the study of patterns of change as well as mechanisms of change and provide an important way for clinicians to contribute to the scientific literature. There are limits to generalizability

⁴¹ Barlow, D. H., & Nock, M. K. (2009). Why can't we be more idiographic in our research? *Perspectives on Psychological Science*, 4, 19-21.

with single-case experiment designs, although these limits decrease with the inclusion of multiple diverse cases.

Question and Answer

In an alternating treatment design approach there is rapid alternation of conditions, which provides an elegant control for threats to internal validity. No baseline is required, and there are no reversals (fewer data points). The conditions need to be randomly alternated on a weekly basis to minimize carryover effects. Dr. Barlow and colleagues are conducting this type of design over 6 weeks to test the mechanism of interest (reduction of experiential emotional avoidance and the associated extinction of anxiety and distress triggered by intense emotional experiences) in different disorders, and then replicating it over several individuals. This design has the advantage of being efficient.

Open Discussion

Moderator: David Barlow, PhD, Boston University

Single-Case Study Designs

Single-case experimental designs might work best with disorders that do not have a strong natural remission curve. In order to be able to turn the effect on and off, there needs to be a reasonable assumption that the disorder is stable in the absence of intervention. Dr. Barlow noted that the one type of single-case experimental design compares alternative treatments and identifies which treatment results in a greater improvement trend. This obviates the issue of a strong remission curve. There are other design options using small sample sizes that do not necessarily require fast alterations or manipulations.

Single-case experimental designs, by definition, do not require large numbers of individuals, but they do allow for a large number of data points.

SMART Designs

SMART designs typically focus on response/non-response as the primary research question. Other tailoring variables can be considered. The SMART design allows for measuring many variables at baseline and intermediate stages. The data then can be analyzed to identify significant moderators that can be tailoring variables for future studies.

The challenge with a SMART design is to balance the complexity of the design with the kind of questions that can actually be answered, and how they inform the intervention development. Dr. Nahum-Shani has found it useful to focus on issues related to the initial stage of the intervention as the primary research question (e.g., behavior modification versus medication).

It is important to note that SMART and factorial designs are both exploratory, not confirmatory, designs. An exploratory design can tolerate a Type 1 error rate of 0.05 for the primary research question.

SMART designs allow for re-randomization of a second-stage intervention based on an intermediate mechanism responsible for subsequent effects for non-responders. Re-randomizing at the second stage can control for various intermediate variables that might affect the outcome of the second stage of an intervention, which makes the case even stronger for addressing selection bias.

Mediators

Participants discussed the utility of conducting a mediation analysis in situations where there is no significant treatment effect. Theoretically, there would be no reason for identifying a mediator for a treatment that does not work. However, given the amount of error possible in using statistical tests to determine the significance of an intervention, the result could be wrong. There have been cases where an intervention does not have an effect but then subsequent studies with greater power do find an effect. Two opposing mediation processes would cancel each other and produce a zero effect. Another reason mediation analysis is useful even in cases where there is no overall effect is that there could be more than one subgroup in the data where the effects work differently.

Incorporating Use-Inspired Basic Research into Research on Effectiveness and Implementation

Testing Theory or Changing the World? Balancing the Competing Goals of Psychotherapy Research

V. Robin Weersing, PhD, San Diego State University

The two central goals of intervention research are to improve public health and test theory. These two goals are in natural tension, and no single study can be designed to fully address both of them. Improving public health includes developing interventions to cure disease and alleviate suffering, improving the quality of health care, and producing practice-relevant knowledge. Testing theory includes testing models of intervention and pathology with the goal of understanding the mechanisms of disease and recovery. The knowledge gained from testing theories may or may not have immediate benefit.

Developing an “Opportunistic” Research Agenda

The tension between these goals is especially apparent when faced with the challenge of designing a research agenda that efficiently builds on the current, large efficacy literature in mental health. Many interventions have been shown to be efficacious in lab-based clinical trials; however, little is known about the effectiveness of these models outside of controlled conditions, and, conversely, little is known about the putative mediators of these interventions. There is a need to develop wise strategies for this “opportunistic” case, because the necessary next steps in research do not neatly fit into translational models based on a phased sequence of

discovery (i.e., basic research stage proceeding through intervention development to public health impact). One key decision that should be addressed is whether research should focus immediately on understanding the public health impact of these treatments or clarifying underlying theoretical issues and basic science mechanisms of action.

The Treatment of Adolescents with Depression Study (TADS)⁴² was used as a cautionary example of how an early move toward questions of effectiveness may be undercut by lack of knowledge on treatment mechanism.⁴³ TADS was designed to be an efficacy-effectiveness trial of CBT, medication, and combination therapy, placing the study on the public health end of the research spectrum. It was thought that CBT had known effects, but the research literature on medication was smaller. Given this understanding, it made sense to focus on the three cells that included combo CBT and medication (CBT and medication; CBT and no medication; no CBT and medication). When these options were compared with pill placebo, it was found that combination CBT-medication had a greater effect than all other configurations and the effect of CBT alone was equal to the effect of the medication placebo. Given the design used in the study, it is very difficult to figure out why this occurred. Perhaps this design did not incorporate the right balance of priorities. For example, there is a great deal of variation in “CBT” techniques for treating adolescents with depression, yet the intervention is considered the same independent variable across studies.⁴⁴ There is also a great deal of variability within individual manuals in how the independent variable is implemented.⁴⁵

The mechanisms of action underlying CBT for depressed adolescents are also unclear. In a review of multiple RCTs, only 1 in 13 assessed behavioral activation and none conducted tests of mediation. Nine of the 13 studies assessed cognitive processes, and only 1 tested mediation with a negative result. Magnitude of cognitive change as an outcome variable is not well connected to the magnitude of depression change. Given the lack of clarity on the IV of CBT and poor understanding of the manner in which CBT may influence outcome, the move toward an effectiveness/ public health design in this area may have been premature, despite a large efficacy literature suggesting that the intervention can produce positive effects.

Balancing Theory-testing and Effectiveness

Although the TADS investigation serves as a cautionary tale for moving too quickly toward public health research, there may be situations in which effectiveness trials can succeed and

⁴² March, J., Silva, S., Petrycki, S., Curry, J., Wells, F., Fairbank, J. et al. (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *Journal of the American Medical Association*, 292, 807-820.

⁴³ See Weersing, V. R. (2006). Testing theory or changing the world? Balancing the competing goals of psychotherapy research. *Clinical Psychology: Science and Practice*, 13, 342-345.

⁴⁴ Weersing, V. R., Rosenman, M., & Gonzalez, A. (2009). Core components of therapy in youth: Do we know what to disseminate? *Behavior Modification*, 33, 24-47.

⁴⁵ Kennard, B. D., Clarke, G. N., Weersing, V. R., Asarnow, J. R., Shamseddeen, W. Porta, G., et al. (2009). Effective components of TORDIA cognitive-behavioral therapy for adolescent depression: Preliminary findings. *Journal of Consulting and Clinical Psychology*, 77, 1033-1041.

also provide data relevant to theory-testing aims. Indeed, two key design features of effectiveness studies may aid in the assessment of mediators and theory-testing aims.

First, designing successful effectiveness trials requires clarity of an intervention model with a constrained number of components that are robust to implementation in practice. Two case examples were provided. One example is a study of efficacy and effectiveness of integrated behavioral therapy for anxiety and depression in the pediatric primary care setting. The initial research focus for this line of work was to better define the core components of CBT by winnowing the range of potential techniques in the literature into a robust package.⁴⁶ Another proposed study is an efficacy and effectiveness trial of attention retraining for youth anxiety within a health maintenance organization (HMO). In this case, the standardized and computerized nature of the intervention provides a uniquely robust IV for investigation in practice and also a clearly defined IV for the purpose of theory-testing.⁴⁷

A second key factor in designing successful effectiveness trials is careful attention to the characteristics of the comparison condition. A treatment-as-usual condition is a complicated but reasonable control that facilitates enrolling in the trial and maintaining public health relevance. Treatment-as-usual can also be a strong theoretical control if there is sufficient evidence that treatment-as-usual is essentially inert for the target condition under investigation. For example, the integrated behavioral therapy for anxiety and depression study uses treatment-as-usual as the comparison, because data from services studies suggests that treatment-as-usual mimics natural remission in this population.⁴⁸ With the attention re-training intervention, treatment-as-usual may be a very weak background intervention, given data on the very low rates of service use by this population.

If careful attention is paid to these study characteristics, then mediation and adherence effects can be shown in dissemination trials. Indeed, understanding the mediator is critical in unpacking the failure of the relationship between an independent and dependent variable and is especially useful if there are variations in adherence, as is common in effectiveness research. Variation in treatment delivery under conditions of practice is a useful predictor, and it avoids ceiling effects associated with the ideal implementation of the independent variable. Furthermore, moderators present in effectiveness samples may highlight mechanism differences within subgroups.⁴⁹ In addition, the large samples involved in effectiveness, implementation, and dissemination investigations have the power to detect interactions and conduct secondary analyses useful for tests of mediation.

⁴⁶ Weersing, V. R., Gonzalez, A, Campo, J. V., & Lucas, A. N. (2008). Brief behavioral therapy for pediatric anxiety and depression: Piloting an integrated treatment approach. *Cognitive and Behavioral Practice, 15*, 126-139.

⁴⁷ See, for example, Rozenman, M., Weersing, V. R., & Amir, N. (2011). A case series of attention modification in clinically anxious youth. *Behaviour Research and Therapy, 49*, 324-330.

⁴⁸ Weersing, V. R., & Weisz, J. R. (2002). Community clinic treatment of depressed youth: Benchmarking usual care against CBT clinical trials. *Journal of Consulting and Clinical Psychology, 70*, 299-310.

⁴⁹ For discussion, see Weersing, V. R., & Weisz, J. R. (2002). Mechanisms of action in youth psychotherapy. *Journal of Child Psychology and Psychiatry, 43*, 3-29.

Question and Answer

Using treatment-as-usual as a comparison group is fraught with issues. Treatment-as-usual can be an ethical and reasonable control if it is the standard of care and there are data that show that it produces not very effective homogeneous results. Treatment-as-usual can provide adequate internal validity and satisfy ethical concerns, but it may also limit the ability to generalize results, especially if there are issues with the external validity of a treatment-as-usual condition in a given study (e.g., access to local or regionally available treatment-as-usual services that are not representative of the population at large).

Designs are typically created with the goal of finding main effects. It is possible, however, to identify mechanisms in a micro-analytic way with an ideal measure (e.g., cognitive change) within the context of a well-designed effectiveness RCT that provides answers about main effects. It was noted that a poor measure (e.g., self-report measure) included in a large sample effectiveness study might be viewed as better than no measure if it has sufficient validity to at least serve as a marker of a possible mechanism effect.

Can Mechanism Be Tested in Effectiveness Trials? Prospect Theory, Loss Aversion, and Regret

Kevin Volpp, PhD, University of Pennsylvania

One challenge of implementation is that an intervention approach could be very well conceptually thought out and efficacious, yet because of complexity or cost, there is no real-world entity in the health system that could or would implement it.

Individual behavior is critical to the health of the population. Behavioral patterns such as obesity, smoking, and adherence account for 40 percent of all causes of premature mortality in the United States (other categories of causes include genetic predisposition, social circumstances, environmental causes, and inadequate healthcare).⁵⁰ Not only do behavioral patterns have such a significant impact on mortality, but also employers report that poor health habits are the greatest challenge to maintaining affordable benefits coverage.⁵¹

Economic models alone incompletely describe human behavior. Economic theory posits that individuals are rational choice-makers and calculate expected utility maximization to inform their behaviors. This view assumes away self-harmful behavior as a function of preferences. Humans are predictably irrational and commit numerous common decision errors: present bias,

⁵⁰ Schroeder, S. A. (2007). We can do better—improving the health of the American people. *New England Journal of Medicine*, 357, 1221-1228.

⁵¹ Towers Watson and National Business Group on Health. (2012). *United States performance in an era of uncertainty: 17th Annual Towers Watson/National Business Group on Health employer survey on purchasing value in health care*. Retrieved February 1, 2013, from <http://www.towerswatson.com/assets/pdf/6556/Towers-Watson-NBGH-2012.pdf>.

nonlinear probability weighting, loss aversion, regret aversion, and making decisions based on emotions.^{52, 53, 54}

Factors other than price are important to influencing health behaviors. Dr. Volpp and colleagues conducted a study with veterans using lotteries and deposit contracts to achieve initial weight loss. The study focused on making the economic incentives more effective. Half of the participants reached their goal in the intervention arms compared to 10 percent in the control group.⁵⁵ Another example is a study of medication adherence (warfarin) using daily lottery-based incentives.⁵⁶ More than 20 percent of historical controls took the incorrect doses compared to 2-3 percent of participants in the daily lottery intervention.

Behavioral Economics

The approach used by Dr. Volpp and his colleagues is to combine decision errors systematically observed across a population and design various aspects of an intervention as specific responses to the particular decision errors. For example, because of present-biased preferences, an intervention should have frequent and immediate rewards. In recognition of the fact that many people overweight small probabilities, an intervention can utilize probabilistic rewards for self-interested behavior. The interventions that result may incorporate several such features, but the relative importance of each component is unclear. Typically employers, insurers, and other entities are not equipped to implement such interventions using their current infrastructure, although this is changing rapidly with the proliferation of wireless technologies and social media.

More specifically, behavioral economics can be used to improve incentive design. Many of the most effective incentive interventions have leveraged multiple decision errors simultaneously. Lottery designs can incorporate nonlinear probability weighting, anticipated regret, present bias, and loss aversion. More information is needed about the specific components, levels of components, and the optimal combination of components needed for an efficacious result. A series of real-world efficacy trials (hybrid efficacy/effectiveness, NIH Stage 3 model) will allow the investigators to simultaneously conduct basic science work and improve intervention efficacy and potential effectiveness and ultimately create interventions that are implementable.

⁵² Thaler, R. H., & Sunstein, C. R. (2009). *Nudge: Improving decisions about health, wealth, and happiness*. New York: Penguin Books.

⁵³ Volpp, K. G., Pauly, M. V., Loewenstein, G., Bangsberg, D. (2009). P4P4P: An agenda for research on pay for performance for patients. *Health Affairs*, 28, 206-214.

⁵⁴ Ariely, D. (2009). *Predictably irrational: The hidden forces that shape our decisions*. New York: HarperCollins Publishers.

⁵⁵ Volpp, K. G., John, L. K., Troxel, A. B., Norton, L., Fassbender, J., & Loewenstein, G. (2008). Financial incentive-based approaches for weight loss: A randomized trial. *Journal of the American Medical Association*, 300, 2631-2637.

⁵⁶ Volpp, K. G., Loewenstein, G., Doshi, J., Troxel, A. B., Price, M., Laskin, M., et al. (2008). A test of financial incentives to improve warfarin adherence. *BMC Health Service Research*, 8, 272-277.

Study Examples

One example of an approach that allows for the deployment of interventions that leverage decision errors is “automated hovering,” which consists of an approach that gets frequent inputs on participant health behavior at home or work using home- and employer-based biometric data collection and gives them different types of feedback.⁵⁷ The approach—an NIH-funded program called Way to Health that is based at the University of Pennsylvania—is designed to automate the process. The participant is given access to a biometric measurement device such as a scale or glucometer, the device transmits information to a server, the server calculates what sort of feedback to send the participant and then sends a text or email or interactive voice message, and incentive funds are transferred electronically to the participant.

To better understand some of the underlying mechanisms for efficacious interventions, a three-arm RCT funded by the National Institute on Aging (NIA) is examining incentives for maintenance among Weight Watchers members who have succeeded in achieving initial weight loss. Daily lottery incentives are being compared to daily fixed payments. The study is being conducted in a real-world setting but still allows for disentangling of components of previously successful interventions. Present bias is addressed, and the feedback frequency is held constant. The study tests the relative value of certainty through daily fixed payments versus the variable reinforcement, nonlinear probability weighting, and the entertainment value that are key components of the lottery design. The goal is to discover if the most effective intervention needs to include a lottery, which is more complex to administer than fixed payments.

A proposed study of brain exercises for older adults includes five experiments that will systematically test lottery incentives in the context of cognitive training exercises. Brain exercises hold promise in their potential ability to reduce the rate of cognitive decline. The goal of this study is to systematically disentangle more complex incentive interventions. This study utilizes the Way to Health platform as well. Cognitive training is important and represents a task that reflects many of the inherent challenges in changing health behaviors: the underlying task is meaningful but requires effort, benefits are delayed and intangible, and there is likely an absence of urgency.

Another approach involves evidence-based evolutionary testing. Dr. Volpp received funding from the Center for Medicare and Medicaid Innovation (CMMI) to test an approach that is based on automated hovering for patients following hospitalization for an acute myocardial infarction. Participants are randomized to a control group or an intervention that will evolve over time as more information is gathered. A series of side experiments will test critical assumptions of the main intervention, which involves social and lottery incentives. Findings from these side experiments will be used to refine the main intervention design in subsequent iterations of the main intervention.

⁵⁷ Asch, D. A., Muller, R. W., & Volpp, K. G. (2012). Automated hovering in health care—Watching over the 5000 hours. *New England Journal of Medicine*, 367, 1-3.

Summary

There is excitement and promise about the potential to change healthcare delivery using insights from behavioral economics. Previous studies have combined multiple concepts as proof-of-concept of power of behavioral economics in changing health behaviors. The next generation of studies needs to help disentangle the relative importance of the different concepts. Given the complexity of implementation, this research and design approach is essential to improving uptake and population effectiveness of interventions.

Question and Answer

Participants found the evidence-based evolutionary testing design approach embedded in the CMMI study particularly intriguing. The design will allow the investigators to learn as the study progresses and incorporate these findings as improvements along the way. There are several interesting considerations with such a design. The study will not be powered to base design refinements on the primary outcome of re-hospitalization rates, but instead will utilize the rate of daily medication adherence in the main intervention, observations about process, and lessons learned from the side experiments that could determine that another design, for example, a social incentive, is more effective than the one embedded in the first version of the intervention.

There is a broad comparative effectiveness research agenda with the goal of determining the relative effectiveness of different interventions. It was noted that Dr. Volpp's research examples in which implementation partners are typically large employers, insurers, or pharmacy benefits managers, are more akin to public health interventions compared to other presenters who focused more at the individual level of intervention. There is a variety of ways to help patients, and both micro- and macro-level interventions are important.

The designs of many of these studies are complex, and currently employers do not typically incorporate such approaches as part of standard benefit design. Ongoing research that incorporates both cost and complexity and that develops automated ways of reducing the complexity of implementation seeks to determine the most efficient ways to incentivize people.

Testing Mechanisms in the Baltimore Experience Corps® Trial

Michelle Carlson, PhD and George Rebok, PhD, Johns Hopkins University

The Experience Corps® program (copyrighted by the American Association of Retired Persons (AARP)) is a model of senior service and health promotion that simultaneously creates generative roles for older adults while meeting unmet needs of public elementary schools. It was designed in 1994 and 1995 and evaluated in 2000-2002. Results of a pilot trial demonstrated Experience Corps®-related improvements among older adults in mobility and executive function among those at highest risk. Volunteers aged 60 and older serve in public elementary schools in kindergarten through third grades. They adopt meaningful roles and address important needs. The model is high intensity because the volunteers work at least 15

hours per week at the schools for 1 school year. Volunteers are reimbursed for their expenses. The seniors are grouped together in a critical mass (20 or more) within each school, allowing them to form a community of volunteers.

A large-scale RCT of the Baltimore Experience Corps® trial, funded by NIA, began in 2006 and concluded in 2011. More than 700 seniors were randomized to either an Experience Corps® school or a low-activity control school and served for up to 2 years. Outcome measures included physical (e.g., disability, mobility, walking speed), cognitive (e.g., memory, executive function), and psychosocial (e.g., depressive symptoms) factors.

The causal pathway for the Experience Corps® is useful for thinking about how the effects of the intervention operate on the senior participants. Intervention participation and generative role performance engages multiple activity pathways to mechanisms—physical, cognitive, and social activity. Mechanisms include strength and balance, brain plasticity, executive function, social integration, and support generativity. The mechanisms can be assessed by performance-based measures of secondary outcomes (e.g., falls, walking speed, frailty, memory, instrumental activities of daily living, psychosocial well-being) and the primary self-report outcome of mobility function.

Children in participating schools also experience activation of primary pathways—academic stimulation, behavioral management, and readiness for learning with academic performance and classroom behavior as the primary outcomes. In addition to individual students, the school community as a whole has the opportunity for primary outcomes as measured by aggregate academic performance, school climate, teacher retention, and volunteer retention. The model creates a win-win situation for all participants.

Examining Mechanisms in an Effectiveness Trial

It is important to examine mechanisms of benefit within the context of this effectiveness trial because benefits might be observed first in intermediate mechanisms and later in behavioral and health outcomes. This is very valuable to the trial. Evidence supports the assertion that brain changes in the hippocampus signal future risk for Alzheimer's disease well before related behavioral changes occur. Biomarkers are very important in diseases such as Alzheimer's because they are early risk factors for preclinical changes in a long disease course.

Evidence supports the possibility of increasing cognitive plasticity in the aging brain through intervention. Enriched environments lead to the creation of new neurons in adult animals, and measurable brain changes have been detected in response to experience.⁵⁸ Changes in neurons and synaptic connections can be seen over the course of 3 to 6 months. Sometimes the change

⁵⁸ See, for example, Briones, T. L., Klintsova, A. Y., & Greenough, W. T. (2004). Stability of synaptic plasticity in the adult rat visual cortex induced by complex environmental exposure. *Brain Research*, 1018, 130-135.
Liston, C., McEwen, B. S., & Casey, B. J. (2009). Psychosocial stress reversibility disrupts prefrontal processing and attentional control. *Proceedings of the National Academy of Sciences*, 106, 912-917.

is not beneficial, such as a social stressor. Research also supports a link between increased physical fitness and hippocampal volume, which is associated with better cognitive health and better maintenance of health.⁵⁹ Examining these changes in the brain is a challenge. It is easy to see how aging affects the functions of most other organ systems, such as hypertension in the heart, reduced skin and muscle tone, and cataracts in the eyes. Studying changes in the brain requires expensive methods that are data intensive and may have high subject burden.

The Brain Health Substudy of 115 participants (average age of 68 years) is nested within the Baltimore Experience Corps® trial and designed to translate these findings of connections between physical activity and brain health into the real world. Findings suggest that even small increases in physical activity may matter. Cross-sectional data show that greater step activity was significantly associated with greater hippocampal volume. The data suggest that even low to moderate levels of activity may help maintain plasticity in a brain structure important to spatial and verbal memory. Pilot data suggest that participation in Experience Corps® over 6 months led to clinically relevant changes in executive function and associated brain regions in the prefrontal cortex.⁶⁰

The goal of the Brain Health Substudy was to examine the direct causal effects of an enriched environment on brain structure and functions. A representative subsample informs the larger behavioral trial by identifying mechanisms. Outcomes of interest included effects on executive function and memory. Intermediate outcomes may precede changes in behaviors. The substudy provided the opportunity to incorporate biologic and physiologic mechanisms that help identify and isolate activity pathways that may mediate and moderate intervention effects, including neuroimaging, salivary cortisol, and fasting blood biomarkers (e.g., lipid levels, glucose, and genetic risk (APOE ε4)). Physical activity is measured by step activity devices.

There are challenges to examining mechanisms within an effectiveness trial. Pilot development is critical to identifying appropriate biomarkers. The cost of intervention administration can be dwarfed by the cost of analysis in trials with substudies.

Question and Answer

The Experience Corps® intervention is an excellent example of getting people into an environment that is social and intensely motivating, which can sustain volunteers' engagement. However, it might be just as important to understand for whom this type of intervention does not provide a motivating environment. The characteristics of non-responders should be explored. Focus groups were held by Dr. Carlson's student over the past 2 years to explore reasons why some participants thrive and some discontinue involvement in Experience Corps®.

⁵⁹ Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., et al. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*, 19, 1030-1039.

⁶⁰ Carlson, M.C., Erickson, K. I., Kramer, A. F., Voss, M. W., Bolea, N., Mielke, M. et al. (2009). Evidence for neurocognitive plasticity in at-risk older adults: The Experience Corps Program. *Journals of Gerontology: Biological Sciences and Medical Sciences*, 64, 1275-1282.

Volunteers sometimes drop out for health reasons or stress. School environments vary tremendously, which can impact participants' decisions to stay. A colleague is further examining volunteer satisfaction in a parallel study with the goal of understanding the factors needed to sustain participation. These findings will be described in two forthcoming companion papers.

Open Discussion

Moderator: Edna Foa, PhD, University of Pennsylvania

Intervention versus Mechanism

There are times when it may be difficult to separate the intervention from the mechanism. Studying mechanisms might be easier within one intervention versus another. Interventions require high fidelity and a clear theoretical understanding of the independent variable-mediator-dependent variable (X-M-Y) relationship in order to examine mechanisms. Complex, multi-component interventions where the relative importance of each component is unclear (e.g., CBT) may be suitable for producing an overall effect size, but can be difficult in terms of identifying mechanisms and the effectiveness of specific components.

Lottery Effects

Dr. Volpp has not seen any evidence of lottery effects subsiding over time. However, a new project involving Weight Watchers participants over a longer period of time will allow the team to test this with more power.

Behavioral economics research is clearly integrated into Dr. Volpp's research on incentives and motivation. Decades of research support schedules of reinforcement and strategies for behavior maintenance, particularly in the private sector (e.g., airlines points systems). While behavioral economics work is foundational, Dr. Volpp and his colleagues are exploring reinforcement systems within a very different context—health insurance or employer-based systems. The goal is to synthesize earlier behavioral economic insights with recent knowledge on predictive rationality.

Meeting participants discussed the likely existence of a plethora of private marketing data on lotteries (e.g., horse racing, McDonald's). Private companies have probably experimented with lottery designs. This is as yet an untapped resource.

Behavior Change versus Maintenance

Incentives and motivation to sustain healthy behaviors will vary depending on the behavior. The desire to be an ex-smoker can be reinforced. Addressing obesity can be more challenging, given that everyone has to eat. The goal with some behavior-related problems, such as obesity, is to teach people more sustainable habits and augment their motivations to stay engaged, rather than simply change individual's calculations of cost-effectiveness.

Behavior maintenance requires a greater understanding of the context and system within which individuals are operating. How the context as a whole (e.g., place of employment, insurance company, school) changes systematically will impact the motivations of the individuals. For example, the school culture has an impact on the motivation of Experience Corps® participants to remain engaged. Another consideration is the role of an individual's personal context, which is rarely addressed in treatment models. An individual could receive an effective intervention in a clinical or workplace setting, but there is little consideration of the role of the home or community environment in maintaining behavior change.

Research on the role of feedback in behavior maintenance is evolving with the advancement of technology and social media. There is evidence that there are different incremental effects of different doses of feedback (e.g., 2 text messages versus 100 in one day). Information provision alone is not that effective for changing behaviors. People require tools and strategies to implement self-control and better manage desires for immediate gratification.

General Discussion

The mechanisms studied today have the potential to be the interventions of tomorrow. One vehicle of innovation can be crossing boundaries and exploring cross-disciplinary themes, strategies, and ideas. The science of behavior change should address dimensions of disorders, specify mechanisms of change, utilize innovative research designs, and design and test interventions that target mechanisms of change in the real world.

Innovative Designs and Review Considerations

Participants discussed the implications of innovative research designs on the review process. Invited speakers were urged to contribute their time as reviewers to bring greater understanding and appreciation of alternative designs (e.g., adaptive randomization, SMART designs) to the review process. Reviewers often view alternative designs as risky and uncertain, especially when in competition with an application using a standard design RCT. Certain mechanisms (e.g., R21, R34) or specific initiatives soliciting high-risk/high-reward research may be more amenable to applications featuring some of the innovative designs presented at the meeting.

Treatment-as-Usual

The definition and usefulness of the notion of treatment-as-usual in research designs continues to be a matter of great debate. Most understand that it can be a valid comparator on some level, yet treatment-as-usual is also problematic. A treatment-as-usual arm must be representative if the goal is to be able to generalize. Large multi-site studies can achieve this representativeness, but also introduce a lot of noise. A strong theory and clearly defined intervention implemented with fidelity is needed in order to detect a signal in a large, multi-site study.

Treatment-as-usual is problematic when it includes many components of varying effectiveness. A decision to include a treatment-as-usual arm must be based on the primary research question. If the research question involves whether it is valuable or cost-effective to change care from treatment-as-usual to a new intervention, then data should be collected on treatment-as-usual. By nature, treatment-as-usual groups are messy; however, a mediation analysis becomes difficult if data are not collected on the treatment-as-usual group.

Heterogeneity of Treatment Response

Heterogeneity of individuals even within a particular diagnosis is a major issue. Individual differences and heterogeneity of treatment response needs to be better understood in order to make meaningful interpretations about how an intervention operates. Research focusing on mediators and mechanisms should help the field refine diagnoses and treatment populations (e.g., psychopathy and externalizing traits).

Revisiting Pasteur's Quadrant: Fostering Use-Inspired Basic Research
The Madison Hotel, Washington, DC
Meeting Agenda

Tuesday, October 9

Dolly Madison Ballroom

8:15 a.m. REGISTRATION CHECK-IN

9:00 a.m. WELCOME REMARKS

Patricia Grady
Richard Hodes
Richard Suzman

9:15 a.m. CHARGE TO THE GROUP

Lisa Onken

**PANEL 1: INCORPORATING USE-INSPIRED BASIC RESEARCH INTO RESEARCH ON
INTERVENTION GENERATION AND REFINEMENT**

Discussion Leader: Timothy Strauman

9:30 a.m. How understanding mechanisms can foster the generation of an efficacious and implementable intervention for the treatment of anxiety

Nader Amir

9:50 a.m. Developing interventions for psychopathic individuals based on an understanding of mechanisms of change

Joseph Newman

10:10 a.m. BREAK

10:40 a.m. Delay discounting and the development of interventions to treat substance abuse

Warren Bickel

11:00 a.m. Empirically grounded treatment generation for insomnia, depression, and bipolar disorder

Allison Harvey

11:20 a.m. OPEN DISCUSSION

12:00 p.m. LUNCH

PANEL 2: INCORPORATING USE-INSPIRED BASIC RESEARCH INTO RESEARCH ON INTERVENTION EFFICACY

Discussion Leader: Richard Bootzin

- | | | |
|------------------|---|-------------------|
| 1:30 p.m. | Mechanism of change in the treatment of depression | Robert DeRubeis |
| 1:50 p.m. | Understanding the mechanism of action of prolonged exposure in the treatment of anxiety | Edna Foa |
| 2:10 p.m. | Where mind meets matter: A translational approach for treating anxiety disorders | Stefan G. Hofmann |
| 2:30 p.m. | OPEN DISCUSSION | |
| 3:10 p.m. | BREAK | |

PANEL 3: EXPANDING METHODS FOR TESTING MECHANISMS OF ACTION

Discussion Leader: David Barlow

- | | | |
|------------------|--|-------------------|
| 3:40 p.m. | What are efficient designs that can help determine essential ingredients of interventions? | Inbal Nahum-Shani |
| 4:00 p.m. | Moderators, mediators, and mechanisms | David MacKinnon |
| 4:20 p.m. | Idiographic functional analysis in treatment development research | David Barlow |
| 4:40 p.m. | OPEN DISCUSSION | |
| 5:20 p.m. | ADJOURN | |

Wednesday, October 10

Dolly Madison Ballroom

9:00 a.m. WELCOME REMARKS Jonathan W. King

**PANEL 4: INCORPORATING USE-INSPIRED BASIC RESEARCH INTO RESEARCH ON
EFFECTIVENESS AND IMPLEMENTATION**

Discussion Leader: Edna Foa

9:15 a.m. Testing theory or changing the world? Balancing the competing goals of psychotherapy research V. Robin Weersing

9:35 a.m. Can mechanisms be tested in effectiveness trials? Prospect theory, loss aversion, and regret Kevin Volpp

9:55 a.m. Testing mechanism in the Experience Corps® trial Michelle Carlson & George Rebok

10:15 a.m. BREAK

10:45 a.m. OPEN DISCUSSION

11:30 a.m. WRAP-UP / CLOSING REMARKS Lisa Onken

12:00 p.m. ADJOURN

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