

National Institutes of Health
National Institute on Aging

Seminar on Loneliness and Social Isolation

The Keck Center of the National Academies
Washington, DC
June 4, 2015

Meeting Summary

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ACRONYM DEFINITIONS

BBCSS	Board on Behavioral, Cognitive, and Sensory Sciences
BSR	Division of Behavioral and Social Research
CBT	cognitive behavioral therapy
EAR	Electronically Activated Record
ELSA	English Longitudinal Study of Ageing
ENRICHED	Enhancing Recovery in Coronary Heart Disease Patients
HRS	Health and Retirement Study
MI	myocardial infarction
MOST	Multiphase Optimization Strategies
NACA	National Advisory Council on Aging
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIH	National Institutes of Health
NRC	National Research Council
SHARE	Survey of Health, Ageing, and Retirement in Europe

MEETING SUMMARY

On June 4, 2015, the National Research Council (NRC) Board on Behavioral, Cognitive, and Sensory Sciences (BBCSS) convened a seminar sponsored by the Division of Behavioral and Social Research (BSR) at the National Institute on Aging (NIA) to solicit expert input on the most promising strategies for advancing intervention development efforts to reduce social isolation and loneliness in mid- to late-life. The seminar included introductory remarks from NIA staff members, four invited presentations, and group discussion. This document summarizes the presentations and discussions that occurred during the seminar. The meeting agenda and participant list are available in the appendices.

Several themes emerged from the presentations and discussions among the invited speakers, board members, and participants.

- Multi-level approaches—at the individual, dyadic, family, community, and population levels—might be needed to understand mechanisms of action and design effective interventions.
- Experimental medicine approaches and optimization methods are well suited for theoretically grounded research to better understand the underlying mechanisms of action for components of an intervention.
- Understanding multifactorial risk may be helpful when designing efficacious interventions.
- Social relationships occur within larger social contexts. A social network itself can serve to promote healthful or unhealthful behaviors.
- Both biological and social trajectories should be considered when determining the optimal type and time in the lifespan for the greatest impact of an intervention.
- The role of social technology needs to be better understood and if possible, leveraged, in the development of interventions.
- Time use data can be used to better understand loneliness and social isolation among older individuals.
- Community involvement and engagement for Stage III research may be critical for certain types of interventions to be implemented successfully and sustained. There is untapped potential in partnering with community organizations for pragmatic trials.
- The workplace is a valuable real-world setting that in some instances can be ideal for testing interventions, particularly those that target individuals approaching retirement.

INTRODUCTORY REMARKS

Novel Interventions to Reduce Social Isolation/Loneliness in Mid- to Late-Life

Lisbeth Nielsen, Division of Behavioral and Social Research, National Institute on Aging

The NIA supports research on the full aging process to contribute to the science foundation for interventions at optimal time points in the lifespan to support healthy aging. The NIA is

interested in exploring the potential of interventions to address social isolation and loneliness, which are both risk factors for poor aging outcomes. Social isolation is the objective physical separation from other people (i.e., living alone), and loneliness is perceived social isolation, or the subjective distressing feeling of being alone, separated, or outcast. Both constructs matter, are moderately correlated, and might implicate different pathways and intervention targets. There are observational data, a growing body of literature, and public health efforts informing novel interventions in this area. A key scientific question is whether social isolation and loneliness are two independent processes affecting health differently, or whether loneliness provides a pathway for social isolation to affect health.

The structural dimensions and quality of interactions in a social network can be measured to assess social isolation. For example, the Survey of Health, Ageing, and Retirement in Europe (SHARE) Social Networks Module uses a name generator approach to capture an ego-centered network.¹ Participants are then asked questions about frequency of contact, emotional closeness, geographical distance, and satisfaction with the network. Social isolation has been linked to health outcomes in a number of ways with these data.

The subjective phenomenon of loneliness can be measured with questionnaires, such as the 20-item University of California, Los Angeles (UCLA) Loneliness Scale or a 3-item scale used in the Health and Retirement Study (HRS). More than 40 percent of adults aged 60 and older participating in the HRS report being lonely at least sometimes. Studies have demonstrated that loneliness can predict cognitive decline, the development of Alzheimer's disease, incident coronary heart disease, and impaired immune responses. Social interactions of those who feel isolated are more negative and less satisfying.

Loneliness and social isolation both predict all-cause mortality in longitudinal studies of aging. Feelings of loneliness were associated with increased mortality risk using HRS data, an effect not explained by social relationships or health behaviors. Analyses of data from the English Longitudinal Study on Ageing (ELSA) demonstrated that both social isolation and loneliness were associated with increased mortality. However, only the impact of social isolation remained significant after adjusting for demographic factors and baseline health.

Experts at a 2012 NRC BBCSS meeting on Motivation and Aging and the 2013 National Advisory Council on Aging (NACA) review of BSR offered several considerations for new intervention research in this area. The BBCSS meeting participants recommended intervening in mid-life, leveraging individual and age differences in motivation and goals, focusing on motives for social belongingness as levers for behavior change, and intervening in networks to leverage the multiplier effect. NACA Review Committee members suggested encouraging collaborations with nonprofit and government groups to increase engagement, focusing on theoretically based intervention designs to elucidate the pathways, and conducting many small studies with short-

¹ Information about SHARE can be found at <http://www.share-project.org>.

term outcomes to target proximal outcomes, such as social isolation, loneliness, and networks, rather than health outcomes to demonstrate the ability to affect the targets.

New intervention research could include:

- Testing a range of pathways to learn about mechanisms
- Conducting small trials before launching larger efforts
- Testing a wide range of activities and designs to attract and affect diverse populations
- Examining how to effectively time interventions in the life course
- Conducting pragmatic trials for scaling up and maximizing sustainability

Approaches could include collaborating with community organizations that engage mid- to late-life adults and embedding interventions into well-characterized samples.

The National Institutes of Health Stage Model

Lisa Onken, Division of Behavioral and Social Research, National Institute on Aging

A behavioral intervention development model that paralleled drug development was first created in the 1990s: create the intervention, test for efficacy, and test for effectiveness. Many efficacious interventions were developed with this model, yet very few were shown to be effective in large-real-world effectiveness trials. Behavioral interventions studied in efficacy trials are typically implemented with a high degree of fidelity. Behavioral interventions could be efficacious but not effective for a variety of reasons that affect fidelity of implementation, including the level of complexity, how difficult the intervention is to learn, and how much training and supervision are required.

Often interventions are adapted—intentionally or unintentionally—when applied to real-world settings. Changing components of an intervention is particularly problematic for behavioral interventions when the mechanism of action is unknown. A greater understanding of mechanisms of action in behavioral interventions should reduce the risk associated with adapting interventions and increase the potency of interventions by preserving and emphasizing the active ingredients in implementation.

Examining mechanisms of action in behavior change involves asking basic science questions within the context of behavioral intervention development. The updated stage model was created to address previous behavioral intervention development failures and to provide a conceptual framework that capitalizes on basic science while striving for optimally scalable interventions.² The stage model, which is consistent with an experimental therapeutics approach, emphasizes theory, the role of basic science, and the importance of understanding underlying mechanisms. Implementability, as well as potency, are the ultimate goals of this

² Onken, L., Carroll, K., Shoham, V., Cuthbert, B., & Riddle, M. (2014) Reenvisioning clinical science: Unifying the discipline to improve the public health. *Clinical Psychological Science*, 2, 22-34.

model. The stage model is translational, iterative and recursive, nonlinear, and non-prescriptive.

The main differences between this model and previous iterations are the greater emphasis on basic science and mechanisms, the broadening of Stage I to address fidelity and implementation issues, and the inclusion of a new Stage III, a hybrid efficacy-effectiveness stage.

1. Stage 0: Basic Research

- a. Basic science that occurs prior to intervention development but is relevant to development.
- b. Research on mechanisms of change-involves asking basic science questions about behavior change within the context of all Stages of behavioral intervention development.

2. Stage I: Intervention Generation and/or Refinement

- a. Stage I studies can be conducted in research or community settings.
- b. All activities related to the creation and preliminary testing of a new behavioral intervention.
- c. Can include the generation of new behavioral interventions as well as the modification, adaptation, or refinement of existing interventions (Stage IA).
- d. Culminates in feasibility and pilot testing (Stage IB).

3. Stage II: Efficacy in Research Settings

- a. Efficacy research consists of experimental testing of promising behavioral interventions in research settings with research-based providers.

4. Stage III: Efficacy in Community Settings

- a. Efficacy in the real world consists of experimental testing of promising behavioral interventions in community settings with community-based providers or caregivers.
- b. A high level of control is maintained to establish internal validity.
- c. This is sometimes referred to as a hybrid efficacy-effectiveness stage.

5. Stage IV: Effectiveness

- a. Effectiveness research examines empirically supported behavioral interventions in community settings with community-based providers or caregivers.
- b. Maximizes external validity.

6. Stage V: Implementation and Dissemination

- a. Implementation and dissemination research examines strategies of implementation and adoption of empirically supported interventions in community settings.

Many efficacious behavioral interventions exist; relatively few are successfully implemented. Ensuring the ease of implementation of an intervention during the intervention development process is essential. Incorporating basic science into the behavioral intervention development process is crucial. Understanding the mechanisms of action facilitates successful

implementation of interventions and can inform approaches to maximize the potency of the intervention.

INVITED PRESENTATIONS

Social Networks and Social Support: Contrasting Observational and Experimental Evidence

Lisa Berkman, Harvard School of Public Health

Berkman presented a nuanced conceptual model to describe how social networks affect health. Social relationships occur within a larger social context. Social and structural factors influence how we develop and maintain relationships and relationship quality. These include culture, economics, geography, social change, and more. The social-structural factors give rise to networks of social relationships, which can be characterized by size, domain, density, reciprocity, social ranking, etc., which are linked to the activation of social networks (e.g., frequency, duration, and intensity of social contact). Social networks provide opportunities for behavioral mechanisms such as social support, social engagement, and social influence. A lack of social support, for example, could lead to loneliness. Social networks themselves are neutral and can promote healthful or unhealthful behaviors. Behavioral mechanisms affect health through psychological, health behavioral, and psychosocial pathways.

Low social support is associated with increased risk for mortality and cardiovascular morbidity. Studies using observational data have demonstrated that those who are married or have a close confidant have better survival outcomes after myocardial infarction (MI). Berkman examined survival by levels of social support in a longitudinal cohort and determined that emotional support was the most important predictor of survival following an acute MI, but social networks were more important in predicting mortality at 7 years post-MI.

The National Heart, Lung, and Blood Institute (NHLBI) supported the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) trial to test the hypothesis supported by observational data that treatment of depression and low social support early after an acute MI reduces death and nonfatal recurrent infarctions.

The ENRICH trial recruited a diverse sample, including an oversample of women and racial and ethnic minorities. The study followed a classic biomedical model to recruit individuals at high risk who were already socially isolated or depressed. The key elements of the intervention were cognitive behavior therapy (CBT) administered with high fidelity, pharmacotherapy, and monitoring and quality assurance. Pharmacotherapy was given to non-responders and those who were severely depressed. There were improvements in the treatment group on social support and depression outcomes between baseline and 6 months. However, the control group also did well. There was no difference in the survival curves between the treatment and control groups from baseline to 48 months, indicating that improvements in social support and depression had no effect on study outcomes. The trial results indicated that treating depression and low social support immediately after MI did not improve medical outcomes.

The well-designed ENRICH randomized controlled trial successfully recruited women and minorities, and demonstrated that the interventions effectively produced a change in the social support and depression measures at 6 months. Yet the trial did not produce the anticipated impact on health outcomes. Berkman surmises that the intervention was not delivered at a biologically important moment. Because mortality from MI most often occurs within the first 30 days post-MI, a 6-month CBT intervention may not be effective in improving health outcomes. In addition to thinking about the appropriate timing for an intervention, it is also important to think about individuals' social trajectories to identify ideal times for people to change their behavior or relationships. Both the biological and social trajectories should be considered when deciding when in the lifespan an intervention could be most impactful.

Loneliness, Isolation, and Experimental Medicine: Building Better Public Health Interventions

David A. Sbarra, University of Arizona

Sbarra challenged participants to think beyond the question of whether social isolation and loneliness differentially affect morbidity and mortality; instead he advocated for building intervention science on an assessment of multifactorial risks. The current approach in behavioral intervention science is to combine multiple elements into treatment packages without using a design that allows for determining the mechanism of action. The optimization of intervention design is needed.

Each component of social connection has a potential mechanism of action that exerts health effects. The constructs need to be broken down and the mechanisms understood. Once this goal is achieved, the elements can be reshuffled for intervention development by focusing on mechanism of action and efficiently optimizing the treatment components. For example, social connection can be broken down into components of structural isolation, relationship functioning/quality, perceived social support, and perceived isolation (loneliness); furthermore, each of these components can have multiple mechanisms.

Sbarra discussed two important Stage 0 and Stage I considerations about risk processes:

- **What is isolation, and are we measuring it properly?** The current understanding of social isolation is limited. For example, in his own work, Sbarra and colleagues are using the Electronically Activated Record (EAR) to sample ambient sounds every 12 minutes for 30 seconds (collected over 2.5 days) at three times across 5 months from recently separated adults. The data are coded for a range of social behaviors, including whether the person is alone. This objective measure of being alone might be the best indicator of isolation. However, a person might be alone but still be socially connected to others in different ways. The number of networks in which people report being involved is not associated with actual time spent alone as measured by the EAR device. These types of relationships need to be clarified.
- **Are the risk indicators *causal* risk indicators?** Co-twin designs are useful in research to study quasi-causal effects. For example, twin data can be used to rule out the influence

of shared genes as a causal effect.³ The co-twin design is useful for showing when putatively causal effects are *inconsistent* with a causal association.

Sbarra proposed experimental medicine methods and Multiphase Optimization Strategies (MOST) for designing social connection interventions.⁴ In experimental medicine, targets of change represent variables that maintain poor health and can be expected to produce positive outcomes when altered. Potential targets for loneliness are hypervigilance to social cues/threats, attentional bias, and behavioral confirmation leading to social skills deficits. Experimentation is critical, as is target engagement. Interventions can be built from the bottom up with a better understanding of how changing a specific target will produce the desired outcome (i.e., which specific components of CBT lead to the outcome versus just CBT). Smaller studies are manageable and can provide a greater return on investment than large trials for these types of experiments.

MOST is a framework for building potent behavioral interventions by using theory to inform the intervention components. MOST is rooted in engineering principles of optimization and evaluation and emphasizes factorial designs. MOST can be used in a top-down approach to dismantle interventions with multiple components. For example, CBT for depression has been dismantled to examine the specific behavior activation component; results demonstrate that the behavior activation component is sufficient to obtain the same outcome for severely depressed individuals without the cognitive development component. In other words, CBT as a whole intervention package is not optimized for severe depression.

In summary, designing efficacious interventions hinges on understanding multifactorial risk. Experimental medicine approaches and MOST methods are ideally suited for a nimble NIH intervention stage model. The field can and should begin with real-world implementation in mind.

Loneliness and Social Isolation

Julianne Holt-Lunstad, Brigham Young University

The NIA is seeking guidance on research that can help resolve whether social isolation and loneliness differentially affect morbidity and mortality through distinct causal pathways and research on interventions targeted specifically at changing loneliness or social isolation, with the ultimate goal of achieving a desirable health outcome. Holt-Lunstad presented results from two meta-analyses to address these issues:

³ McGue, M., Osler, M., & Christensen, K. (2010). Causal inference and observational research: The utility of twins. *Perspectives on Psychological Science*, 5, 546e-556e.

⁴ Collins, L. M., Murphy, S. A., Nair, V. N., & Strecher, V. J. (2005). A strategy for optimizing and evaluating behavioral interventions. *Annals of Behavioral Medicine*, 30, 65-73.

See also <http://methodology.psu.edu/ra/most>.

1. The first meta-analysis focused on social relationships and involved 148 studies and 308,849 participants followed for an average of 7.5 years.⁵ Those who were more socially connected had a 50 percent increased odds of survival compared to less socially connected individuals. Results of the analyses indicated that social connections have a profound effect on physical health and longevity and that the magnitude of effect is comparable to leading health indicators such as physical activity, body mass index, and smoking cessation. Identifying the causal mechanism(s) of this effect is critical.
2. The second meta-analysis focused on social isolation, loneliness, and living alone and included 70 studies of more than 3 million participants followed for an average of 7 years.⁶ Social isolation, loneliness, and living alone were found to be associated with a 30 percent increased likelihood of mortality, and there were essentially no differences in the associations between mortality and subjective or objective measures of isolation. This does not mean that these constructs are interchangeable; one hypothesis is that each has differential risk associated with it. For example, a person can be isolated but not feel lonely, and a person can feel lonely but not be isolated.

These findings have implications for intervention design, suggesting that both functional and structural aspects of relationships are important for increasing survival odds and that both objective and subjective measures of social isolation are significant predictors of premature mortality. Intervention design might benefit from a multifactorial risk assessment. Interventions that only address one risk component without regard to the others may have unintended negative effects. Complex social integration represents multiple components of relationships, including a diversity of relationships that would tap into many pathways.

The data did not provide evidence of a threshold effect. Social isolation and loneliness were not stronger predictors than other indicators of social connections. The effect of complex social integration was significantly stronger than social isolation, loneliness, and living alone. The protective/positive effects of social relationships should be considered as well. Taken together, these data also suggest that interventions need not be limited to older adults. Targeting individuals across the risk trajectory earlier in the life course may be useful for prevention. Just as with other areas of public health, prevention via encouraging healthy lifestyles could potentially have a greater impact than addressing an existing problem later.

Holt-Lunstad proposed examining multifactorial risk as well as using multi-level approaches to understand mechanisms and to design effective interventions. The individual, dyadic, family, community, and population levels can all be considered. The mechanisms might operate at different levels and suggest different types of interventions to be implemented in a stage model.

⁵ Holt-Lunstad, J., Smith, T.B., & Layton, B. (2010). Social relationships and mortality: A meta-analysis. *PLoS Medicine* 7(7), e1000316.

⁶ Holt-Lunstad, J., Smith, T.B., Baker, M., Harris, T., & Stephenson, D. (2015). Loneliness and social isolation as risk factors for mortality: A meta-analytic review. *Perspectives on Psychological Science*, 10, 227-237.

Technology is changing the ways in which individuals interact socially. The internet and mobile technology are now the primary means of communication. This shift is likely to continue. Whether this type of social media interaction has the same kinds of effects as other types of social interaction needs to be explored. Interventions should not be designed based on the assumption that social media and face-to-face interactions are equivalent. Social technology may accelerate and accentuate existing processes. It is possible that social technology could make social individuals more social and isolated individuals even more isolated, which would have implications for intervention design.

In summary, the greatest needs in intervention development include multifactorial risk assessment and a better understanding of the role of social technology. A metric, such as the Framingham Coronary Heart Disease Risk Score, could be developed to enable clinicians and other health professionals to identify an individual level of risk. A multi-level approach should be used to understand mechanisms. Individual differences can contribute to the development of personalized interventions at some levels (i.e., person level).

Targeting the Right Aspects of Social Relationships in Intervention Studies

Andrew Steptoe, University College London

Observational studies have demonstrated associations between loneliness, social isolation, and a range of health outcomes. However, there is a danger in moving from observation to intervention prematurely. It is unclear whether interventions are needed that target loneliness and social isolation separately. Loneliness interventions aim to develop and strengthen close personal bonds, but are not necessarily targeted at a large group of individuals. Social isolation interventions might focus on increasing contacts and engagement across a wider network, but the type of contact might be superficial.

Different health outcomes might be associated with different aspects of social relationships. In Steptoe's own work using ELSA data, social isolation as an independent factor, rather than loneliness, predicted all-cause mortality after controlling for preexisting poor health, wealth, education, marital status, and ethnicity. Recent work on dementia has highlighted loneliness and close personal relationships rather than social isolation. Unpublished analyses of ELSA data have shown an association between loneliness and an increased risk for dementia, controlling for demographic factors and initial cognitive status. These analyses suggest that selective targeting of loneliness and social isolation for particular health outcomes is complicated.

Intervention research with older individuals has generated some promising results; but some of the studies were poorly designed and had variable impacts. Stronger effects are found in institutional rather than community samples; that is, when the intervention is carried out in a care home or other institutional setting, possibly because there is greater fidelity to the intervention program in these situations. Interventions tend to focus on social skill development or cognitive behavioral interventions targeting thought processes. Both are promising avenues with different implementation considerations. Cognitive behavioral

interventions tend to involve intensive interaction with participants, which makes them difficult to deploy on a large scale.

Stephoe noted that sex differences might have implications for interventions, particularly among older individuals. Broadly speaking, women tend to communicate face-to-face, and men tend to communicate side-by-side. That is, men tend to embed personal interactions within a shared external activity (e.g., watching sport, doing a hobby) rather than in a setting deliberately set up for communication.

An approach that might improve understanding of the underpinnings of interventions is to better assess time use in relation to loneliness and social isolation among older individuals. Lonely individuals aged 65 and older spend nearly 8 hours alone at home each day compared to 2.5 hours for those who are not lonely. Lonely individuals spend 90 percent more time in health activities, 20 percent more time watching TV, and 30 percent less time volunteering. Lonely individuals have a diminished interest in activities compared to non-lonely individuals, and loneliness in older people is strongly linked with boredom. This information could be used to design a population-based intervention to reduce TV-watching by 30 minutes and replace it with a different, more social, activity.

DISCUSSION

The discussion, moderated by meeting chair Susan Fiske, focused on three questions posed to the invited speakers and Board members.

1. How can early-stage intervention development studies (e.g., Stage I) inform the science? What can be gained through studies with shorter-term outcomes, targeting social isolation, loneliness, and networks rather than health to demonstrate the ability to affect these targets?
2. What is the role of mid-stage intervention development studies (e.g., research-based Stage II and community-based Stage III efficacy trials with maximal internal validity)? How can theories best be tested, and how can questions of mechanisms of behavior change best be built into these studies? How can mid-stage efficacy trials be designed to identify responders and non-responders?
3. Where has the groundwork been laid for late-stage intervention development studies (e.g., Stage IV effectiveness trials with maximal external validity)? That is, are there efficacious interventions where there is also evidence that they can be efficaciously delivered in real-world settings; and if so, are these interventions ready for effectiveness trials? For efficacious interventions being considered for effectiveness trials, have issues of dosage (i.e., frequency, intensity, and duration) been sufficiently addressed, with respect to fidelity of implementation and in achieving targeted outcomes? How can effectiveness studies be designed to shed light on the mechanisms that account for response effects?

Early-Stage Intervention Development Studies

There is no single intervention that addresses the multi-dimensional constructs of social isolation and loneliness. Interventions that target multiple levels might be needed. Stage I work is critical for demonstrating that a particular intervention or manipulation can produce the desired change in a specified target in multiple domains. It might be particularly important for Stage I studies to examine short-term outcomes of social relationships, including biomarkers and other intermediate markers of health.

Theoretically grounded research is needed to better understand the underlying mechanisms of action of an intervention. An intervention to build senior housing may be effective for a variety of reasons (e.g., physical proximity, exercise, help with manual tasks, social interaction, sense of belonging to a tribe). Hypotheses about the underlying mechanisms need to be explicitly tested in early-stage studies (as well as later-stage studies) to identify common mechanisms and to determine explicitly what works for whom and why, and under what circumstances. One outcome of interest should be specific mortality rather than all-cause mortality; social isolation resulting in lack of prompt medical care is different from social isolation and depression increasing the risk of poor health outcomes.

Participants discussed the need for both individual- and population-level approaches. There are multiple levels at which relationships can potentially affect health (e.g., individual, dyad, family, community) and there could be different mechanisms involved at each level that need to be targeted differently. Population- and policy-level interventions have the potential for widespread effect and sustainability, especially if they involve behavioral nudges within naturally occurring social networks. Individual-level interventions, such as CBT, focus on remedying a skills deficit in the individual. The intervention approach should be designed based on the desired targets and the needs of the population.

There does not appear to be a threshold effect for social isolation and loneliness, but rather a gradient effect. Social networks are complex and function well over time for complex reasons. For example, there will be a point at which it does not matter whether an individual has 6 or 15 friends, but the difference between having zero and 2 friends is likely critical.

Participants discussed social isolation as a risk factor for poor health outcomes, social connectedness as a potential protective factor, and the measurement issues raised by considering these two perspectives. It is possible that time use research could provide insight on these complex issues.

It would be useful to have a multifactorial risk assessment with a metric to identify who might be at risk of health consequences from social isolation or loneliness. An agreed upon metric and standard (e.g., such as the Framingham risk score) could be valuable because the variety and variability of current measurement approaches can be interpreted as a lack of precision.

Mid-Stage Intervention Development Studies

Identifying biomarkers and understanding the multiple pathways by which an intervention works is important for research-based Stage II and community-based Stage III efficacy trials. A complex intervention can operate along different behavioral or physical pathways. Community involvement and engagement at Stage III can be critical for translation and sustainability of certain types of interventions. Interventions tend to stall at Stage II because of the difficulties of demonstrating efficacy in real-world settings (Stage III).

Work at this stage can advance understanding of whether observational data are indicative of a causal effect or a proximal variable that is driving the effect. For example, rather than set out to design a mindfulness intervention that aims to prevent or cure cancer, Stage II and III intervention development studies can identify the proximal outcomes that are affected by the intervention to better understand the pathway. Observational data can support a hypothesis that then needs to be deconstructed and tested experimentally to identify the mechanisms and relationships. Understanding the underlying mechanism and the theory that explains the relationship tells us what the intervention should be (e.g., a pet, a phone, a dishwasher, social interaction). The MOST framework and experimental medicine methods are useful for testing small-scale theories that can identify the mechanism(s) of action.

Participants discussed the importance of Stage III community-based intervention development and noted that there is untapped potential in partnering with community organizations for pragmatic trials. Many community organizations are interested in engaging with researchers and are willing to have control groups. There are community-based trials happening already, including those focused on the benefits of volunteer work to older adults.

Participants agreed that the workplace is a valuable real-world setting in which interventions could be tested. Individuals spend a great deal of time in a workplace, and the setting comprises its own social network, shapes individuals' opportunities for family and community networks in complex ways, and has multiple organizational structures. The workplace is an ideal setting to test preventive interventions earlier in the life course, to determine long-term effects of these interventions, and to intervene specifically during the transition from the labor force to retirement. The workplace environment could be used to provide nudges toward maintaining activity and social interaction into retirement.

Funding agencies could encourage and shape the structure of desired research by providing guidance or requirements for building community partnerships and intervening in particular real-world settings. For example, the R21/R33 funding mechanism could be used to achieve this goal; the R21 phase would focus on developing community partnerships and demonstrating mechanisms of action at the community level, and the R33 phase would focus on optimizing and testing the intervention in a community-based trial. MOST methods could be used in an experimental add-on to an existing community-based program or intervention.

Late-Stage Intervention Development Studies

Holt-Lunstad noted that data from a preliminary meta-analysis of interventions and their impact on mortality suggest that interventions involving a combination of individual skills building (professional component) within existing meaningful relationships (family social interaction component) are the most successful.

Early interventions can have powerful effects on outcomes later in life, which could be examined using secondary data and data linkages. For example, Berkman completed a difference-in-difference analysis on the impact of maternity leave policies in Europe on women's depression 30 years later using secondary data and found effects that were not apparent at the time of the policy. One area of investment could be adding or harmonizing a module on social relationships and/or life histories in longitudinal cohort studies to allow for these types of secondary data analyses on long-term effects at the population level. Other topics related to social isolation that could be explored this way include retirement and cognition, impacts of national retirement policies, social engagement or social support in retirement, defined contribution versus defined benefit retirement policies, and financial advice before or during retirement.

Population-based interventions or policies can have a widespread effect, but studies might also focus on individual differences and intervening on particularly vulnerable populations. For example, adult caregivers may lose part of their social networks because of the intense demands of caring for a spouse. After the loss of a spouse, caregivers have higher levels of depressive symptoms and rate themselves lonelier than non-caregivers.

Participants posited that existing measures of constructs related to social isolation and loneliness are quite good. However, there are many measures and the field as a whole is difficult to distill. Mechanistic work is missing from these efforts; as a result, there is very little current understanding of the causal relationships and what target needs to be changed in order to affect an outcome. For example, what is the best way to intervene on hypervigilance to social cues—cognitive reappraisal, decentering, more activation, or something else? Experimental medicine methods can be used to identify the mechanism of action, which would point to the appropriate intervention approach. The conceptual framework needs to specify the mechanism and how a particular intervention approach addresses it.

Concluding Remarks

Nielsen reiterated that the NIA is interested in identifying ways to improve the quality of life throughout the aging process. In the process of building a causal theory, the NIA hopes to identify the gaps that need to be filled and the opportunities that are ripe for investment. Onken noted that questions remain about the mechanism of action for these constructs, for example, how and to what extent social isolation and loneliness are related to morbidity and mortality. The field appears to be ready for theory-driven Stage I research to identify and examine the mechanisms that can then inform interventions to manipulate targets. In addition, research to decompose the mechanisms and active ingredients is particularly important because existing data suggest that multicomponent interventions yield the strongest effects.

Research at Stages I, III, and IV can leverage partnerships with community organizations and existing community-based interventions in real-world settings.

**APPENDIX 1
MEETING AGENDA**

**BOARD ON BEHAVIORAL, COGNITIVE, AND SENSORY SCIENCES
NATIONAL RESEARCH COUNCIL**

Seminar on Loneliness and Social Isolation

June 4, 2015
Keck Center, Room 105
500 Fifth Street NW
Washington, DC 20001

- 1:00 *Welcome to the National Academies*
Barbara Wanchisen, Director, BBCSS
- 1:10 *Setting the Stage for the Seminar*
Susan Fiske, Chair, BBCSS
- 1:25 *Introductory Remarks from the National Institute on Aging (NIA)*
Lis Nielsen & Lisa Onken, Division of Behavioral and Social Research, NIA

Panel Presentations: Each panelist is allotted 15 minutes to answer the questions provided in advance by the NIA, highlighting relevant information from his or her field or his or her work in particular.

- 1:45 *Panel Presentations*
Lisa Berkman, Harvard University
David Sbarra, University of Arizona
Julianne Holt-Lunstad, Brigham Young University
Andrew Steptoe, University College London (via web conference)
- 2:45 **BREAK**
- 3:00 *Panel Discussion: Each of the Three Questions Will Be Covered in Turn*
Susan Fiske, moderator
- 4:30 *Conclusions, Final Thoughts, Next Steps*
Susan Fiske, moderator
Lis Nielsen & Lisa Onken, NIA
- 5:00 **ADJOURN**

APPENDIX 2

LIST OF PARTICIPANTS

Invited Speakers

Lisa Berkman, Harvard University
Julianne Holt-Lunstad, Brigham Young University
David Sbarra, University of Arizona
Andrew Steptoe, University College London (via web conference)

Members of the Board on Behavioral, Cognitive, and Sensory Sciences

Susan T. Fiske, Chair, Princeton University
Laura L. Carstensen, Stanford University
Jennifer Cole, University of Illinois at Urbana-Champaign
Judy R. Dubno, Medical University of South Carolina
Robert L. Goldstone, Indiana University
Nina G. Jablonski, Pennsylvania State University, University Park
James S. Jackson, University of Michigan
Janice Kiecolt-Glaser, The Ohio State University College of Medicine
Bill Maurer, University of California, Irvine
John Monahan, University of Virginia
Steven E. Petersen, Washington University Medical School
Dana M. Small, Yale Medical School
Timothy J. Strauman, Duke University
Allan R. Wagner, Yale University
Jeremy M. Wolfe, Harvard Medical School

National Institutes of Health Staff

Melissa Gerald, National Institute on Aging
Jonathan W. King, National Institute on Aging
Lisbeth Nielsen, National Institute on Aging
Lisa Onken, National Institute on Aging
Jerry Suls, National Cancer Institute

National Academies Staff

Tenee Davenport, National Research Council
Barbara A. Wanchisen, National Research Council
Tina Winters, National Research Council

Other Participants

Suzanne Austin, Research Councils UK in the United States
Beth Casey, AARP Foundation
Nancy Gee, State University of New York, Fredonia
Karyl Hurley, Mars Incorporated

Chandra Keller-Allen, Rose Li and Associates, Inc.
Kamili Wilson, AARP Foundation