National Institutes of Health
OppNet

Office of Behavioral and Social Sciences Research (OBSSR)

Research on Biopsychosocial Factors of Social Connectedness and Isolation on Health, Wellbeing, Illness, and Recovery: Second Annual Virtual Grantees Meeting

May 18–19, 2023
Meeting Summary

DAY 1
Welcome and Overview
Liz Necka, Ph.D., National Institute on Aging

Dr. Necka welcomed the participants to the second annual investigators meeting for the OppNet [NIH Basic Behavioral and Social Science Opportunity Network] Social Connectedness and Isolation Initiative. OppNet is a collaborative initiative that includes the NIH Office of the Director and the 24 institutes and centers (ICs) that support and administer research projects. OppNet identifies crosscutting basic social and behavioral research areas and issues notices of funding opportunities (NOFOs) to stimulate projects that complement the interests and missions of the ICs. Management, operational, and financial support for OppNet is provided by OBSSR.

The participants in this meeting were principal investigators, co-investigators, and trainees on projects funded through the Research on Biopsychosocial Factors of Social Connectedness and Isolation on Health, Wellbeing, Illness, and Recovery initiative, a series of funding opportunities issued in 2019 to research the underlying mechanisms, processes, and trajectories of social relationships and how these factors affect outcomes in human health, illness, recovery, and overall well-being.

Additional attendees were funded through a similar initiative, the Dyadic Interpersonal Processes and Biopsychosocial Outcomes initiative, which invited basic and methodological research projects to illuminate or measure independent and interdependent health-related effects within dyads. Both funding opportunities acknowledged the importance of social connection and health but noted that more research is needed to better understand the mechanisms by which social connection and health are related. OppNet supports basic research, recognizing that before interventions can change health, researchers first must understand how the social factors affect outcomes in health, illness, recovery, and overall well-being. Research communities and the general public are increasingly acknowledging the importance of

this issue, and the COVID-19 pandemic accelerated interest in understanding how social connections affect health.

This meeting was designed to illuminate opportunities for collaboration, as outlined in the NOFO. NIH is not prescribing future steps but providing the opportunity for researchers to benefit from shared expertise and distinct contributions of colleagues to drive the science of social connection and social isolation.

Data Blitz
Moderator: Karen Bales, Ph.D., University of California, Davis
The data blitzes consisted of five 5-minute presentations on projects funded through these initiatives. In the first session, Dr. Patricia Kinser outlined a study of social connectedness for marginalized pregnant women with depression. Their pilot work suggested that social connectedness may be one mechanism through which a yoga-based intervention can be effective for this population. John Paulus, Claudia Manca, and Alita D. Almeida presented on studies to investigate kappa opioid and oxytocin interactions in social buffering and partner separation in nonhuman primates; imaging results showed signal displacement in regions implicated in social connectedness, which was consistent with results of other nonhuman primate studies.

Dr. Jessica Andrews-Hanna outlined a study of dyadic empathy for healthy relationships. Preliminary experiments have shown that feedback directed only toward a partner activates regions associated with cognitive and empathic concern, but when the subject receives negative feedback and the partner receives positive feedback, other activated regions may support the ability of the subject to overcome the self and feel good for their partner. Dr. Jenny Tung presented on a long-term observational study of wild baboons. Previous evidence has shown that social relationships are reflected in molecular patterns of gene expression and regulation; the project focuses on characterizing the gene regulatory signatures of social relationships at the time of sampling and aligning them with the social history of each animal across its life span.

Dr. Meghan Meyer explained a study in which people who reported greater loneliness also had more idiosyncratic representations of cultural touchstones (e.g., celebrities) in a brain region reliably implicated in social knowledge. Communication, which helps people feel connected to others, is thought to help align the types of shared realities these participants lack.

Prenatal Social Connection and Disruption During the COVID-19 Pandemic: Effects on Maternal and Infant Health
Darby Saxbe, Ph.D., University of Southern California
Dr. Darby Saxbe described the Coronavirus, Health, Isolation, and Resilience in Pregnancy (CHIRP) study, launched in spring 2020, which gathered reports from expectant parents on their feelings of social connectedness and support during their pregnancies. The study also will test the effects of the pandemic on infant development. The significance of the work lies in its potential to help researchers better understand mental health, and the developmental risks associated with stress and resilience during

pregnancy may serve as an evidence base for future treatments and interventions. The transition to parenthood is a time of change across multiple domains, including alterations to the structure and function of the brain. Times of change can bring risk as well as offer opportunities, and these can translate to many aspects of health. Some risk factors in this time may be modifiable.

Dr. Saxbe's laboratory runs a longitudinal study that follows expectant parents across the first year postpartum to examine adjustment to parenthood at the brain and hormonal levels. This study was halted in spring 2020 because of the COVID-19 pandemic, causing the researchers to consider the challenges for expectant and new parents navigating the heightened need for social support and connection during a time when the sudden advent of lockdowns disrupted prenatal health care and support from extended family. In the first wave of the cohort, participants shared many disruptions in their lives, changes in social contact across all domains, and alarming levels of distress. Prenatal stress is known to be a predictor of postpartum parental mental health and infant early development. These trends continued over time, showing significantly greater depressive symptom endorsement at every time point for the pandemic-exposed cohort.

Women who reported greater decreases in social contact early in the pandemic delivered infants with lower birthweights, which seemed to be driven by an increase in maternal depressive symptoms resulting from decreases in social contact. Dr. Saxbe's team also plans to assess whether geographical differences in COVID-19 case rates influenced the mother's experience during the pandemic. The team may also investigate how the shift to a chronic phase of the pandemic has affected flexibility in the workplace and time with infants and children, as well as how the pandemic may have changed parents' division of labor or plans to have additional children.

Discussion

- Dr. Saxbe commented on the learning curve required to convert the laboratory study to a remote study, such as the difficulty in getting participants to return hair samples to test for cortisol. She commented that because hair grows slowly, the samples provide a cumulative cortisol output that requires less sensitivity.
- When asked if the team reviewed protective factors, Dr. Saxbe agreed that much of the research on the pandemic has shown that risks are very differential and that disparities are prevalent.
- Dr. Saxbe explained that the original study was restricted to cisgender mixed-sex couples because the study included gonadal hormones, but CHIRP had a broader group of participants. The data analysis was restricted to cisgender birthing parents to compare more directly with the earlier cohort, but assessing the effects on sexual and gender minority participants will be important in the future.

How Discrimination Gets Under the Skin: Perspectives from the Brain and Gut Microbiome
Arpana Gupta, Ph.D., University of California, Los Angeles
Dr. Arpana Gupta outlined her project focused on investigating how social isolation and discrimination affect the brain and microbiome. Discrimination is associated with many poor health outcomes, but a full understanding of the mechanistic pathway is lacking. Health is coordinated by a tightly regulated balance between intestinal and extra-intestinal homeostatic and non-homeostatic mechanisms, whereas disease shifts toward non-homeostatic mechanisms. The brain–gut microbiome system has concurrent signaling between the brain and the gut; both also are influenced by the environment. Recent studies in Dr. Gupta's laboratory demonstrate evidence for alterations in the brain–gut microbiome system related to discrimination; the studies found differences between the high-discrimination and low-discrimination groups on every measure, and all ethnicity groups reported the same levels of discrimination, although the reasons for discrimination varied significantly. The studies revealed novel associations between a history of discrimination and alterations within the brain, gut microbiome, and immune system.

Discrimination affects multiple aspects of the body and human health, and a history of discrimination is related to alterations in brain networks related to emotion and cognition. These studies show that the structural and functional changes in the gut microbiome are suggestive of systemic low-grade inflammation. Discrimination related to race or skin color led to changes in the brain and a microbiome that skewed toward inflammation, whereas discrimination related to other factors that may become more prominent as people age were associated with anxiety, emotional arousal, and depression, but not with inflammation, suggesting that people can develop flexibility with a cognitive understanding of the discrimination (e.g., Chen et al., 2023; Guan et al., 2023; Kilpatrick et al., 2023; Osadchiy et al., 2023).

Brain–gut microbiome and immune differences are more prominent when stratified by race and ethnicity, suggesting initial evidence that may explain how discrimination contributes to health inequalities and disparities. Experiences of discrimination also affected cravings for unhealthy sweet foods, suggesting that experiences of discrimination might alter communication between the brain and gut in response to different foods and lead to unhealthy food choices and future obesity. These findings provide a preliminary framework for understanding how discrimination is perceived and processed in the brain and how this is related to inflammation and changes in the gut microbiome, providing a preliminary understanding of how social inequalities become a whole-body experience and how discrimination has a physical manifestation in the body.

Discussion
- In response to a question about whether the studies of face perception indicate that people who have experienced discrimination have difficulties with face perception, Dr. Gupta explained that most past studies of face perception look at it from the perspective of the perpetrator; this study looks at the perspective of the victim and

suggests that there is a dysregulated or increased connectivity with other networks, causing a disrupted fight-or-flight response.

- When asked about sex differences, Dr. Gupta commented that these studies are in progress but noted that women tend to show differences in the emotional arousal network and use food for comfort, whereas men receive hormone levels from the bottom-up signaling of the gut microbiome.
- Dr. Gupta acknowledged that multiple oppressions could overlap and indicated that intersectionality could be studied in the future.

Speed Networking

Attendees rotated randomly through several virtual breakout rooms to discuss a given question; these sessions were designed to promote communication among scientists at all levels and foster future collaborations.

Breakout Session 1

Attendees gathered in breakout groups to discuss what is currently needed regarding social connectedness research. Group 1 focused on complexity, noting that research has one starting point and many endpoints, and systems often need to be considered as dynamic. Context is important, but individual differences can be seen, even in very social animals.

Group 2 discussed measurement of social connectedness, including objective versus subjective measures, emerging technology, and timescales. Dr. Dave Sbarra pointed out that one benefit of this group is its shared expertise in measurement and paradigms; communicating these common understandings to other researchers could help expand the network.

Group 3's discussions centered on how animal research can answer questions that cannot be accessed with human research and the human problems that lack animal models, and Group 4 focused on the gaps between human and animal fields. Both groups acknowledged the need for more communication between animal researchers and human researchers, who may be using different terms for similar concepts. Dr. Bales emphasized that the need for shared language and mutual education is a recurring theme.

Group 5 discussed the benefits and drawbacks of various technologies on social connections and how processes regulated by in-person interaction may be affected by the shift to virtual connections. They also discussed how to compare the effects of virtual and in-person interventions. Group 6 also discussed technology, including how the COVID-19 pandemic increased telehealth options, especially for underserved populations, but that more research is needed. Recent developments in artificial intelligence have transformed some aspects of research development, but some gaps remain. Group 6 also discussed the larger social ecology and cultural context in which these technological developments occur and how technological advances can affect politics or how people interact. Dr. Sbarra noted that researchers still lack an understanding of how co-regulatory processes operate in person, which makes defining

what is lost in virtual communication difficult, but knockout paradigms could be considered. He emphasized that social neuroscience is a multilevel theory with many intervention points.

DAY 2: May 19, 2023

Dr. Necka reviewed the Surgeon General's advisory on the epidemic of loneliness and isolation, which outlines a national strategy to advance social connection. The advisory recommends that researchers prioritize social connection research, develop a cross-disciplinary research agenda, and focus on the root causes of social disconnection and how it influences risk and resilience for health and other societal outcomes.

Data Blitz
In the second data blitz, Dr. Kim Miller outlined her team's study on social health activity behaviors and quality of life among cancer survivors ages 15 to 39. This study focuses on the trajectories of social factors after a diagnosis and assesses interrelations with other key processes, activities, and behaviors. The team hypothesizes that increasing symptom burden could lead to social withdrawal, reducing activity behaviors and further increasing symptom burden.

Dr. Jamil Zaki presented on a study of social network factors and mental health among young adults, noting that data from thousands of college freshmen showed higher than expected mental health experiences. Negative mental health experiences were linked to lower numbers of direct social ties among college freshmen, even before the COVID-19 pandemic (Courtney et al., 2023). Nourishing peer connections can buffer people from stress; Dr. Zaki's team is working to combine social network, psychological, and brain-based methods to quantify social predictors of well-being. Findings from the most recent cohort showed that the number and strength of friendships can have positive mental health effects for years.

Isabela Cruz-Vespa presented on a study investigating whether social connection protects against substance abuse, particularly for those who experience secondhand exposure to racism, such as witnessing someone else be targeted by racial discrimination. The team found that Black survey respondents who reported higher vicarious racism showed more substance use, but this was moderated by ethnic identity, suggesting that ethnic identity is protective for Black participants. This association was not found in Latinx participants, so future directions could include identifying points of intervention that could be protective for the health of marginalized populations, such as bolstering ethnic identity.

Dr. Kate Lapane presented on contextual social isolation—having a socially salient characteristic in a context in which few other people share that characteristic—in nursing homes, especially during the COVID-19 pandemic. Residents who were contextually isolated were more likely to develop depression.

Keynote Address
Julianne Holt-Lunstad, Ph.D., Brigham Young University
Dr. Julianne Holt-Lunstad discussed the Surgeon General's Advisory on the Healing Effects of Social Connection and Community and highlighted the effort made to ensure it represents the evidence across disciplines in a way that is accessible to the public. Although the COVID-19 pandemic brought greater awareness to the issues, they are not new; the pandemic tested society in ways for which it was not prepared, exacerbating an existing problem, highlighting gaps, and challenging the ability to mobilize in a crisis. Social connection often is underappreciated but has been shown to be critical for individual and population health. Evidence points to dysregulation across multiple biological systems when societal needs are not met, and if this dysregulation is sustained over time, it can lead to the development of disease. Social connection in early life and adulthood is one of the strongest predictors of morbidity and mortality risk across social species.

Clearly defining the work has been a challenge; researchers use many terms, but the general public focuses primarily on loneliness, and the term is used to describe many kinds of social isolation. Dr. Holt-Lunstad proposed an umbrella term of "social connection" to encompass the structural, functional, and quality aspects of connections. Each indicator of connection has not been highly correlated with predictors of risk and protection, suggesting that each may contribute in unique ways. Data suggest a continuum from risk to protection, but most interventions are designed only for individuals on the extreme end of the spectrum, meaning even successful interventions reach only a small population. Societal-level approaches also are needed; focusing on the protective effects of social connection as part of prevention may allow population-level risks to be shifted. Evidence can be applied to advance population health through the health sector, such as by encouraging health care providers to ask patients about their social relationships and considering social relationships as an aspect of personal health. Various sectors of society need to be engaged; many opportunities for effecting change with transdisciplinary approaches remain untapped. The Surgeon General's advisory recognizes that reduced social contact affects all sectors of society, suggesting that every sector plays a role.

A culture of connection, in which the informal practices of everyday life significantly influence social relationships, is needed, as is deeper knowledge. The Surgeon General's advisory takes a life course approach and points to the role that all can play, but it will need sustained effort to achieve success. Dr. Holt-Lunstad challenged attendees to consider their roles and how they can begin to take action.

Discussion
- In response to a question about how younger people can replace social media with more lasting forms of connection, Dr. Holt-Lunstad agreed that many are currently grappling with this issue. Although the effects of social media connections are unclear, evidence exists for the benefits of in-person connections.
- When asked to explain the loneliness epidemic in terms of culture, Dr. Holt-Lunstad pointed out that decades of data show that connections have been decreasing. She

theorized that this is related to the conveniences of modern society that reduce the need to rely on others, which decreases interactions with people from different backgrounds.

- In response to a question about system-level initiatives in other countries, Dr. Holt-Lunstad noted that the national strategy calls for government leadership positions at many levels and reiterated that although this has long been viewed as a personal issue, system-level changes are needed.

Effects of Altering Social Connectedness on Health
Jessica Vandeleest, Ph.D., University of California, Davis
Dr. Jessica Vandeleest explained that many interventions designed to improve social connections for commensurate improvement in physical and mental health often are studied in high-risk populations and in the context of existing disease. This leads to a lack of understanding of the basic mechanisms that link changes in sociality due to an intervention with the underlying processes that link these changes to health. Her team is working to bridge this gap using a nonhuman primate model. Their interventions aim to increase affiliative connections among rhesus macaques and determine whether those connections lead to a change in health, as well as observe whether the social or physiological effects persist if the intervention is removed.

In the first intervention, some infant macaques, are placed in foster care to assess the effects of these changes on the community. In the second experiment, a lower-ranking macaque that was trained to open a box of treats received more affiliative behaviors but also exchanged more subordination signals, showing that it had become densely embedded in the social network. The team plans to repeat this experiment with additional macaques in different social groups. In all studies, the researchers also are examining biomarkers and veterinary records.

Discussion
- When asked why the grooming patterns did not change during the intervention, Dr. Vandeleest pointed out that the short duration of the intervention may affect some of the results. There also may be individual differences in whether changes in social context are desired.
- Dr. Vandeleest clarified that the subordination network is not perfectly associated with rank; the individual macaque in the intervention did not change its position but became more closely embedded in the signaling system that supports the network and reinforced existing positions. She pointed out that the researchers also will assess the effects of ending the intervention.
- In response to a question about whether resource leveraging is common in macaques, Dr. Vandeleest commented that macaques in the wild may excel at finding food sources, which could lead to more affiliation from other individuals.

Breakout Session 2
In the second breakout session, participants discussed how to create a sustainable research network and what the desired outcomes would be. Group 1 suggested that a sustainable network would include ways to easily identify other investigators with similar interests. An organizing committee might be valuable for providing structure. Group 2 agreed that both top-down and bottom-up levels of organization would be necessary, and in-person meetings would have value. Activities with defined goals might be more productive.

Group 3 discussed how to better establish a directory of collaborators and potential outlets for such collaborations and noted that identifying ways to connect researchers with related interests would be helpful. They also suggested a newsletter that could highlight project milestones and public commentaries to disseminate research findings. Group 3 also noted that trainees often are helpful for encouraging collaborations. Group 4 pointed out that a website with a tab for trainees could help bring them into the network. Conferences could incorporate time for trainees to try any of the methods discussed, and a "speed dating" system for trainees and investigators could be designed.

Discussion
- Dr. Necka encouraged attendees to consider which ideas are actionable and who might champion them, whether they are R01-based teams or NIH program directors.
- Dr. Sbarra commented that participants have permission to champion any aspect of these ideas to begin moving the process forward and can take over any portion of a particular effort. Participants also have permission to contact one another regardless of career level and invite involvement.
- Trainees might have more time and motivation, so providing explicit ways for them to connect may facilitate other network connections.
- Making connections may require rethinking ways to identify and communicate with researchers.
- Participants expressed enthusiasm for a future in-person meeting with the full group or topic-based subgroups. The scientific community lacks consensus on whether in-person meetings should resume, but this meeting could be scheduled to occur before another conference that many participants may also attend. Dr. Necka pointed out that because this group of investigators is very diverse, an in-person meeting risks excluding people who are unable to travel.
- The next meeting could be a working meeting or focus on subgroups; the format could be changed depending on what would be most useful to the investigators. Multiple shorter meetings also could replace the longer annual meeting, and smaller groups may be more likely to make progress.
- A simple survey, which NIH could help facilitate or the scientific organizers could develop, could help match researchers for future collaborations.

Planning the Next Meeting
Meghan Meyer, Ph.D., Dartmouth University, and Arpana Gupta, Ph.D., University of California, Los Angeles
Dr. Meyer commented that although planning for the next meeting has not started, participants agreed that an in-person aspect to the next meeting is desired and that collaborations could be facilitated through a website or newsletter. Participants also emphasized that trainees should be involved and that publicizing opportunities for funding, such as NIH's funding for short course development, would be helpful.

Concluding Remarks and Dismissal
Arielle Gillman, Ph.D., National Institute of Minority Health and Health Disparities
Dr. Arielle Gillman identified common themes of the meeting, including the desire for in-person opportunities, enthusiasm for an online platform with connection opportunities, interest in having the annual meeting be driven by investigators to create more of a working meeting, and considering the involvement of trainees throughout these efforts. She encouraged attendees to engage NIH to support these efforts as appropriate.

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