NIH National Institutes of Health

NIH Music and Health

Relating Target Engagement to Clinical Benefit

Biomarkers for Brain Disorders of Aging

SOUND HEALTH

Wednesday
August 25, 2021

1:00-5:00 p.m. ET

U.S. Department of Health & Human Services
National Institutes of Health

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Foreword From Dr. Francis Collins

My passion for music began as a boy growing up on a Virginia farm. One of my pleasures throughout my career has been performing with colleagues and meeting other amazing artists. But my personal delight in music and my scientific endeavors have generally occupied different times and spaces. That all changed when I met Renée Fleming at a dinner event a handful of years ago. We quickly discovered a shared interest in the power of music and its role in health and healing, and how that might connect with the rapid progress being made in neuroscience.

In her role as the best-known operatic soprano of our current era, and mine as the Director of the National Institutes of Health (NIH), we had both heard anecdotes about the effects of music on learning, the mind, recovery from illness, reduction of stress, language skills, etc. But the time seemed right to explore the connections between music and the mind more deeply, and in a more coordinated fashion. The outgrowth of those fortuitous conversations with Ms. Fleming, who is now a friend and sometimes co-performer, was the founding of the Sound Health Initiative, a collaborative effort of NIH and the Kennedy Center for the Performing Arts, along with our colleagues at the National Endowment for the Arts. This initiative has led to many wonderful things, including scientific workshops, community activities, performances with a focus on sharing the science of music, the development of NIH funding opportunities, the awarding of numerous research grants exploring the effects of music, and the formation of the Sound Health Network. For our part at NIH, we have formed the Trans-NIH Music and Health Working Group, which brings together scientific leaders from across NIH to discuss and advance research into music and health.

At today's meeting, *Relating Target Engagement to Clinical Benefit—Biomarkers for Brain Disorders of Aging,* the third in a series of three, the Trans-NIH Music and Health Working Group will shift its focus to the important topic of biomarkers. In partnership with the Renée Fleming Foundation and the Foundation for the NIH, the working group hopes to create a core dataset of biomarkers to be used in future NIH-funded music-based intervention protocols. Expert panel discussions of considerations for selecting biomarkers will be the heart of this meeting. In addition, multidisciplinary panelist teams will present ideas for prototype projects (case studies) based on the principles presented in the three workshops. These demonstration projects will provide an early opportunity to test the toolkit that the working group is developing.

I want to thank the many panelists who have gathered today to share their expertise in neuroscience, music therapy and music medicine, behavioral intervention development, clinical trial methodology, and patient advocacy and arts-based organization leadership. A special thanks to Mr. Alan Weil, editor of *Health Affairs,* for serving as our facilitator for this important dialogue. Many thanks to all of you for joining us and sharing your questions. I wish this team success in their discussions, and look forward to seeing the toolkit for research on music-based interventions for brain disorders of aging take shape as a means of advancing the field of music and health research.

Francis Collins, M.D., Ph.D.
Director, National Institutes of Health

Foreword From Renée Fleming

On some level, I have always been aware of strong connections between health and the arts. Building technique for classical singing is a physical process requiring years of practice, coaxing involuntary muscles to cooperate in the creation of a highly cultivated sound. For stage performers, anxiety can abound, and singing live before thousands of people (and critics) made me intensely cognizant of the mind-body connection. I have observed firsthand the powerful effect that music can have on listeners' emotions.

But I really became fascinated by this area when I noticed coverage in the press of the use of music by neuroscientists to explore brain function. It was extraordinarily compelling to me to discover this neurological connection.

To my extreme good fortune, at about that time I found myself in company with one of the great scientists of our time, Dr. Francis Collins. I was delighted to discover that he was also a musician; and before long, our shared interest in music and health led to the launch of the NIH Sound Health collaboration with the Kennedy Center (where I am an artistic advisor), with the participation of the National Endowment for the Arts.

It was a steep learning curve for me, once I found myself at a conference table with Dr. Collins at NIH, listening to presentations by researchers and music therapists. That's when I learned how much there was still to accomplish, and the very granular research needed in this field. Since then, I have become increasingly active in my advocacy. On my concert tours across North America and around the world, it has been both a privilege and a thrill to offer presentations at local health care institutions, universities, and performing arts centers, inviting scientists, physicians, and practitioners to share their research and experience with the general public and each other.

In my discussions at NIH and on my travels, I encountered a recurring theme, an issue that was mentioned both by institutional leaders and individual researchers. A common stumbling block in the practical advancement of this work is the variable quality of research. There is a pressing need for enhanced data collection, with guidelines for scientifically rigorous studies—essentially, a "toolkit" for investigators. Research that is acceptable to NIH is crucial in order to develop evidence-based clinical trials of music and arts therapy interventions. Stringent standards of inquiry can also help dispel an outdated misconception that this area is "soft science."

So, I am honored and excited that the Renée Fleming Foundation can contribute to this effort, supporting the initiative, "Developing Evidence-Based Music Therapies for Brain Disorders of Aging." I am profoundly grateful to Dr. Collins and the many brilliant researchers and administrators at NIH for finding common purpose. And I send thanks in advance to all the panelists and observers for this convening and others held earlier this year. Your dedication to this work is inspiring.

Renée Fleming, Renowned Soprano, Arts and Health Advocate

Agenda

August 25, 2021: 1:00–5:00 p.m. ET

1:00–1:10 p.m. **Welcome**

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health (NIH)

1:10–1:15 p.m. **Opening Notes to Music-Based Interventions for Brain Disorders of Aging**

Coryse St. Hillaire-Clarke, Ph.D., Program Director, Sensory and Motor Disorders of Aging Program, Division of Neuroscience, National Institute on Aging

1:15–1:40 p.m. **Biomarkers: Key Instruments for Music-Based Interventions in Aging**

Steve Hoffmann, M.S., Associate Vice President, Research Partnerships, Foundation for the NIH; Director, Biomarkers Consortium

Presentation (20 minutes)

Question and Answer Session (5 minutes)

1:40–1:50 p.m. **Charge to Panelists and Thematic Group Discussion Setup**

Emmeline Edwards, Ph.D., Director, Division of Extramural Research, National Center for Complementary and Integrative Health

Alan Weil, M.P.P., J.D., Editor-in-Chief, *Health Affairs*

1:50–2:20 p.m. **Question 1:** Music-based interventions have the potential to manage symptoms, slow disease progression, rehabilitate, and improve quality of life. Knowing that important domains of brain disorders of aging are emotion, cognition, and motor and sensory function, what are important considerations for selecting biomarkers for Alzheimer's disease and Alzheimer's disease–related dementias, Parkinson's disease, and stroke?

2:20–2:50 p.m. **Question 2:** What types of biomarkers (predictive, prognostic, diagnostic, disease progression, treatment response) could be linked to clinical outcomes in music-based interventions for Alzheimer's disease and Alzheimer's disease–related dementias, Parkinson's disease, and stroke?

2:50–3:10 p.m.

Question 3: In music-based intervention protocols, can we identify markers that are associated with biological effects and clinical benefits?

Examples of behavioral and biological markers (nonexhaustive):

- Receptor occupancy (positron emission tomography [PET])
- Hippocampal volume (structural imaging)
- Engagement of relevant brain systems (functional magnetic resonance imaging [fMRI], clinical electrophysiology—electroencephalography [EEG], frequency-following response [FFR], neurocognitive performance, and emotional reactivity)
- Body sway (ecological momentary assessment [EMA], sensor and mobile technologies)
- Blood/cerebrospinal fluid (CSF) markers (e.g., CSF {beta}-amyloid 42 and tau proteins)
- Retinal and/or skin biometric responses
- Genetic/epigenetic markers
- Markers of affect (tone of voice) and nonverbal communication (facial expression)

3:10–3:20 p.m. **Break**

3:20–4:25 p.m. **Demonstration Projects**

Presentation by multidisciplinary panelist teams of prototype projects (case studies) applying the principles discussed in the three convenings.

Project 1: Music-based interventions for early- and/or midstage Alzheimer's disease and Alzheimer's disease–related dementias, addressing behavioral and psychological symptoms of dementia (BPSD)

Project 2: Music-based interventions for Parkinson's disease, addressing both motor and nonmotor symptoms

4:25–4:55 p.m. **Broad Question and Answer Session**

NIH VideoCast audience and Zoom meeting participants

4:55–5:00 p.m. **Wrap-Up and Next Steps**

Robert Finkelstein, Ph.D., Director, Division of Extramural Activities, National Institute of Neurological Disorders and Stroke

Guiding Principles for the Choice of Biomarkers

Guiding principles and practical implementation considerations in choosing biomarkers associated with biological effects and clinical benefits:

- The research question, the types and goals of the intervention, and the patient and caregiver experience (population and disease condition) are primary determinants in the choice of biomarkers.
- Basic auditory perception, musical experience, individual choice of music, and other contextual factors (e.g., culture, clinical setting) should be considered.
- The stage of the disease and disease outcomes (behavioral issues such as agitation, frustration, and/or high levels of anxiety) may impact data collection of biomarkers; biomarker collection is more difficult in mid-to-late-stage dementia.
- Identifying the specific domains (sensory, emotion, cognition, motor) affected by the disease condition is a strong consideration. It is important to assess the impact of the music intervention on multiple domains, i.e., the Thinking-Moving-Feeling triad.
- The time dimension is critical; investigators should choose a biomarker with a temporal resolution that allows detection in the time course of the trial.
- Practical factors such as overall cost and resource requirements (e.g., the investigative team's expertise, infrastructure) should be considered.
- The impact on subject burden should be considered.
- It is important to consider the caregiver–subject dyad and the impact of the intervention on both (important factors: burnout, empathy, stress relief, engagement, adherence, at-home practice, etc.).
- The risk/benefit ratio of the music-based intervention should be seriously considered (potential risks with symptom exacerbation—anxiety produced by exposure and expectations of skill learning, risks of falls and fractures).
- Technological tools and applications should be incorporated into music-based interventions (e.g., digital measures for facial expressions and movements, wearable devices for sleep quality, activity level, exposure to music, heart rate variability; phone apps for reminders and in-home practice; ecological momentary assessment (EMA) methodology; actigraphy; voice recording; video recordings).

Potential Biomarkers To Be Considered When Designing Music-Based Inventions for Brain Disorders of Aging

Category	Potential Biomarkers	Methodological Examples (Nonexhaustive)
Inflammation	High-sensitivity C-reactive protein (hs-CRP), proinflammatory cytokines, e.g., interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha)	Bioassay (enzyme-linked immunosorbent assay [ELISA])
Brain structure	Gray and white matter density, structural connectivity	Magnetic resonance imaging (MRI)
Neural circuits and function	Functional activation and functional connectivity	Functional MRI (fMRI), electroencephalogram (EEG)
Neurotransmitter dynamics	Neural receptor occupancy	Positron emission tomography (PET), electrophysiology
Neurotransmitter dynamics	Dopamine transporter (DAT)	Neurotransmission imaging
Neuroplasticity	Brain derived neurotrophic factor (BDNF)	Bioassay (ELISA)
Neurotransmitter dynamics	Dopamine (DA)	Neurotransmission imaging and levels of DA contained in tears or blood
Neurodegeneration	Neurofilament light chain (NFL-1), alpha-synuclein, tau	Bioassay (ELISA, real-time quaking-induced conversion [RT-QuIC] assay, etc.)
Neurodegeneration	Amyloid and tau	PET
Gene expression	Presenilin 1 gene methylation, alpha-synuclein DNA methylation	Blood and saliva collection
Affective	Tone of voice, quality and control of voice, facial expression	Audiovisual recordings
Affective (anxiety and agitation)	Cortisol level, adrenocorticotropic hormone (ACTH), noradrenaline, leptin, proinflammatory cytokines, e.g., IL-6, TNF-alpha	Bioassay (ELISA)
Affective	Activation in dopaminergic reward system	fMRI
Affective	Connectivity between auditory and reward systems	fMRI
Affective (autonomic arousal)	Galvanic skin response, pupil diameter, heart rate variability	Skin electrodes and pupillometer
Affective (social engagement)	Eye contact, synchronization of body sway across participants	Visual and motion capture (eye tracking, video, wearables)
Affective (social engagement)	Oxytocin	Bioassay (ELISA)
Sensory	Auditory frequency-following response (FFR)	EEG
Sensory	Rhythmic entrainment	EEG, Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
Motor	Body sway, mobility	Biometrics, MDS-UPDRS, wearables
Motor	Speed of movement	Timed tapping, timed up and go, timed walk; wearables, etc.

Abstract for Steve Hoffmann's Presentation

Steve Hoffmann, M.S., Foundation for the National Institutes of Health

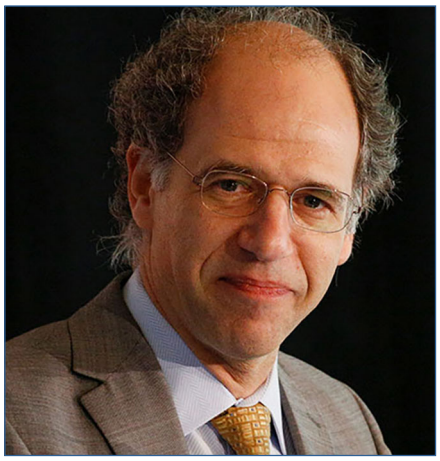
Steve Hoffmann, M.S., is an associate vice president in research partnerships and director of the Biomarkers Consortium at the Foundation for the National Institutes of Health (FNIH). He provides strategic planning, programmatic management, and research administration of a multifaceted portfolio of established and emerging projects within the Biomarkers Consortium and Accelerating Medicines Partnership, including projects involving neuroscience, rare diseases, organ toxicity, infectious disease, and other autoimmune and inflammatory diseases. Mr. Hoffmann has a broad background in the academic, government, and industry sectors in the field of translational biomarkers, molecular immunology, and precision medicine. Prior to joining FNIH, he worked as both a project and product manager, supporting protein diagnostics development at Meso Scale Discovery (MSD). Before MSD, Mr. Hoffmann was a scientist in the Transplantation and Autoimmunity Branch of the National Institute of Diabetes and Digestive and Kidney Diseases and led research efforts utilizing immune depletion and costimulatory blockade strategies for human renal and islet cell transplant trials. Mr. Hoffmann holds a Master of Science degree in pathology and laboratory medicine from the University of North Carolina at Chapel Hill and a Bachelor of Science degree in biochemistry and biophysics from the University of Pittsburgh.

Biomarkers: Key Instruments for Music-Based Interventions in Aging

Healthy aging and well-being are lifelong goals for every one of us. With increasing elderly populations worldwide, the recognition that much of the cost of health and personal care is concentrated in the last decades of life further emphasizes our need for better tools and interventions to modulate the risk of age-related frailty, disability, and disease. Music is increasingly thought of as beneficial for health; however, the scientific research supporting this claim is not yet entirely robust. Music-based assessments, or biomarkers, of cognition, behavior, motor function, and mood may be good measures of the effects of nonpharmacologic/psychosocial interventions during aging. As underscored by this meeting, a critical next step is to conduct the rigorous, evidence-based analytical and clinical validation to support regulatory decision making and precision medicine. Biomarkers have become an increasingly impactful part of both drug development and medical practice and have been defined as "a characteristic that is measured and evaluated as an indicator of normal biologic processes, a pathogenic process, or pharmacologic responses to a therapeutic intervention." This presentation will provide a high-level understanding and key considerations of the evidentiary criteria and framework necessary to advance biomarkers and outcome measures for use in clinical trials and practice. In addition, how best to utilize these measures and approaches for music-based interventions for brain disorders and aging will be further highlighted. Harmonizing scientific and clinical expertise with novel tools and interventions will help us better conduct the orchestra of beneficial next steps needed to improve the quality of life for all.

Facilitator and Panelist Biographies

Facilitator



Alan Weil, J.D., M.P.P., *Health Affairs*

Alan Weil, J.D., M.P.P., became the editor-in-chief of *Health Affairs* in 2014. For the previous decade, he was the executive director of the National Academy for State Health Policy, an independent, nonpartisan, nonprofit research and policy organization. Previously, he directed the Urban Institute's Assessing the New Federalism project, one of the largest privately funded social policy research projects ever undertaken in the United States; held a cabinet position as executive director of the Colorado Department of Health Care Policy and Financing; and was assistant general counsel in the Massachusetts Department of Medical Security. Mr. Weil is a frequent speaker on national and state health policy, Medicaid, federalism, and implementation of the Affordable Care Act. He is the coeditor of two books, publishes regularly in peer-reviewed journals, has testified before Congress more than half-a-dozen times, and is called upon by major media outlets for his knowledge and analysis. He earned his bachelor's degree from the University of California, Berkeley, a master's degree from Harvard's Kennedy School of Government, and a J.D. from Harvard Law School.

Behavioral and Social Science Intervention Development

Bryan Denny, Ph.D., Rice University

Bryan Denny, Ph.D., is an assistant professor of psychological sciences at Rice University and director of the Translational Social Cognitive and Affective Neuroscience Lab. He received his B.A. in psychology in 2005 from Stanford University and his Ph.D. in psychology in 2012 from Columbia University. He completed postdoctoral training in translational applications of social cognitive neuroscience at the Icahn School of Medicine at Mount Sinai before coming to Rice University in 2016. His work seeks to understand the psychological and neurobiological mechanisms underlying emotion regulation. In 2018 he was named a Rising Star by the Association for Psychological Science.

Sona Dimidjian, Ph.D., Renée Crown Wellness Institute and University of Colorado Boulder

Sona Dimidjian, Ph.D., is director of the Renée Crown Wellness Institute and professor, Department of Psychology and Neuroscience, at the University of Colorado Boulder. Dr. Dimidjian received her B.A. in psychology from the University of Chicago and a Ph.D. in clinical psychology from the University of Washington. Her current research projects focus on preventing depression and supporting wellness among new and expectant mothers, promoting healthy body image and leadership among young women, and enhancing mindfulness and compassion among youth, families, and educators. Dr. Dimidjian has a longstanding interest in expanding access to, scaling, and sustaining effective programs, using both digital technology and community-based partnerships.

Eric L. Garland, Ph.D., L.C.S.W., University of Utah

Eric L. Garland, Ph.D., L.C.S.W., is the distinguished endowed chair in research, an associate dean for research, and a professor at the University of Utah College of Social Work. He is also the director of the Center on Mindfulness and Integrative Health Intervention Development and the associate director of integrative medicine for the Supportive Oncology and Survivorship Center at the Huntsman Cancer Institute. Dr. Garland is the developer of an innovative, multimodal, mindfulness-based intervention founded on insights derived from cognitive, affective, and neurobiological science called Mindfulness-Oriented Recovery Enhancement (MORE). As a principal or coprincipal investigator, he has received nearly $50 million in research grants from a variety of prestigious entities, including NIH, the U.S. Department of Defense, and the Patient-Centered Outcomes Research Institute. He conducts translational research on biopsychosocial mechanisms implicated in stress and health, including randomized controlled trials of MORE as a treatment for prescription opioid misuse and chronic pain conditions. In recognition of his national expertise in mindfulness research, in 2019, Dr. Garland was appointed by NIH Director Francis Collins, M.D., Ph.D., to the multidisciplinary working group of NIH HEAL (Helping To End Addiction Long-term^{SM}) Initiative. Dr. Garland served as past chair of the research working group of the national Academic Consortium for Integrative Medicine and Health. Dr. Garland has had more than 160 scientific articles and book chapters published in respected, peer-reviewed outlets, and he currently serves as associate editor for the journal *Mindfulness*. To complement his expertise in clinical research, Dr. Garland is a licensed psychotherapist with more than a decade of clinical experience working with persons suffering from addictive behaviors, mood disorders, traumatic stress, chronic pain, and psychosomatic conditions. He has provided mindfulness-based therapy, cognitive behavioral therapy, and clinical hypnosis for these patients across a wide range of integrative medicine and mental health settings.

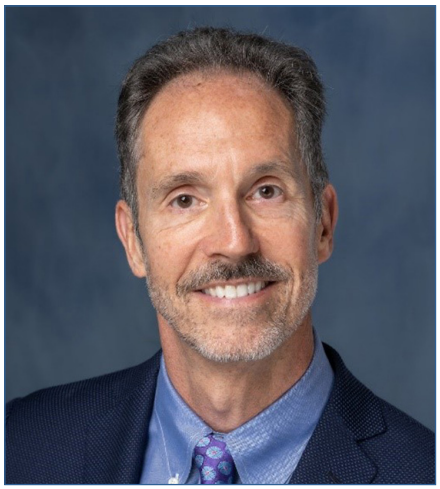
Assal Habibi, Ph.D., University of Southern California

Assal Habibi, Ph.D., is an assistant research professor of psychology at the Brain and Creativity Institute at the University of Southern California. Dr. Habibi is an expert on the use of electrophysiologic and neuroimaging methods to investigate human brain function. She has used longitudinal and cross-sectional designs to investigate how music training impacts the development of children from underresourced communities, and how music generally is processed by the body and the brain. Her research program has been supported by Federal agencies and private foundations including NIH, the National Endowment for the Arts, and the GRoW @ Annenberg Foundation. Her findings have been published in peer-reviewed journals including *Cerebral Cortex, Music Perception, Neuroimage,* and *PLoS ONE*. Currently, Dr. Habibi is the lead investigator of a multiyear study, in collaboration with the Los Angeles Philharmonic and its Youth Orchestra program (YOLA), investigating the effects of early childhood music training on the development of brain function and structure as well as language skills and cognitive, emotional, and social abilities. Dr. Habibi is a classically trained pianist and has many years of music teaching experience with children, a longstanding personal passion.

Susan Landau, Ph.D., University of California, Berkeley

Susan Landau, Ph.D., is a research neuroscientist in the Helen Wills Neuroscience Institute at the University of California, Berkeley. Her research focuses on the transition between normal aging and dementia using neuroimaging and other biomarkers of Alzheimer's disease pathophysiology. She works in the positron emission tomography imaging core for several multisite imaging studies and trials, and she is principal investigator of the U.S. POINTER imaging ancillary study, which aims to understand how lifestyle interventions influence Alzheimer's brain biomarkers and cognition in at-risk older adults.

Clinical Trials Methodology



Roger B. Fillingim, Ph.D., University of Florida

Roger B. Fillingim, Ph.D., is a distinguished professor at the University of Florida (UF) College of Dentistry and the director of the UF Pain Research and Intervention Center of Excellence. He also serves as director of the UF Center for Advancing Minority Pain and Aging Science. Dr. Fillingim's research investigates biopsychosocial mechanisms mediating individual differences in pain, including racial and ethnic disparities in pain as well as age-related changes in pain processing. His work includes mechanistic clinical trials for chronic pain conditions. Dr. Fillingim's research program investigating individual differences in pain has been continuously funded by NIH for more than 25 years, and he currently holds multiple grants from the National Institute on Aging. He has published more than 390 scientific articles and is a frequent speaker at national and international conferences.

Kenneth E. Freedland, Ph.D., FAHA, FABMR, Washington University in St. Louis

Kenneth E. Freedland, Ph.D., FAHA, FABMR, is a professor of psychiatry and psychology at Washington University School of Medicine in St. Louis and the program director of the 2021 Summer Institute on Randomized Behavioral Clinical Trials. Dr. Freedland has served on the faculty of the annual Summer Institute since 2007. He is an expert in the selection and design of comparators for health-related behavioral trials and in the role of feasibility studies and pilot trials in behavioral intervention research. He chaired the NIH/Office of Behavioral and Social Sciences Research Expert Panel on Comparator Group Selection in Behavioral and Social Science Clinical Trials and was the principal developer of the Purpose-Guided Trial Design (PGTD) framework. He has also served on the Single-Site and Pilot Clinical Trials (SSPT) study section and the multicenter Clinical Trials Review Committee (CLTR) for the National Heart, Lung, and Blood Institute, in addition to other grant review committees and special emphasis panels. He has also been a principal investigator or coinvestigator on both single-site and multicenter trials of behavioral interventions. His research focuses primarily on the role and treatment of depression, stress, and anxiety in patients with heart disease, and he has been involved in clinical research on patients with other chronic medical conditions as well. Dr. Freedland was an associate editor of *Psychosomatic Medicine* for over 10 years, chaired the Publications and Communications Council of the Society of Behavioral Medicine, is the associate editor for behavioral medicine for the Hogrefe series on *Advances in Psychotherapy: Evidence-Based Practice,* and is the editor-in-chief of *Health Psychology*. He is a fellow of the American Heart Association and of the Society of Behavioral Medicine, a founding

fellow of the Academy of Cognitive Therapy, a former member of Council of the American Psychosomatic Society, past chair of the American Heart Association's Behavior Change Committee, and past president of the Academy of Behavioral Medicine Research.

Sheri L. Robb, Ph.D., M.T.-B.C., Indiana University

Sheri L. Robb, Ph.D., M.T.-B.C., is a professor at the Indiana University (IU) School of Nursing with international recognition for her expertise in pediatric music therapy and behavioral intervention research. She is a member of the IU Simon Comprehensive Cancer Center and director for the Indiana Clinical and Translational Sciences Institute (CTSI) KL2 Young Investigator Program, and she serves on the Sound Health Network leadership team. Dr. Robb is a board-certified music therapist with degrees in music therapy and early childhood special education. She completed an R25 postdoctoral fellowship in behavioral oncology and cancer control at IU, followed by a KL2 training award in clinical and translational research from the Indiana CTSI. Dr. Robb's research program focuses on development and testing of music interventions to manage distress and improve positive health outcomes in children and adolescents with cancer and their caregivers. Most recently, her team has begun incorporation of biomarkers to understand more fully how active music interventions work to mitigate cancer-related stress and their potential to improve immune function. Dr. Robb is an established investigator with 15 years of continuous funding from NIH, including the National Institute of Nursing Research, National Cancer Institute, and Children's Oncology Group. She also led publication of *Reporting Guidelines for Music-Based Interventions* to address calls for more transparent and accurate reporting in music intervention research.

Caroline M. Tanner, M.D., Ph.D., University of California, San Francisco/San Francisco Veterans Affairs Health Care System

Caroline M. Tanner, M.D., Ph.D., is professor, Department of Neurology, Weill Institute for Neurosciences, University of California, San Francisco, and associate director for research, Parkinson's Disease Research, Education, and Clinical Center, San Francisco Veterans Affairs Health Care System. Dr. Tanner specializes in movement disorders in her clinical practice. Her research interests include investigations of the descriptive epidemiology, environmental and genetic determinants, biomarkers, early detection, and nonmotor disease features of movement disorders and trials for their secondary prevention, disease modification, and symptomatic treatment. She is past cochair of the Parkinson Study Group and has conducted numerous clinical trials. Dr. Tanner and her colleagues have identified associations between environmental exposures including certain pesticides or solvents

and increased risk of Parkinson's disease (PD) and gene-environment interactions. Her current research interests include the use of technology to increase participation in clinical research. She leads the Fox Insight online study and is a member of the leadership team of the Parkinson's Progression Markers Initiative (PPMI) study, which includes prospective online data collection. She is coprincipal investigator of the NIH-sponsored TOPAZ (Trial of Parkinson's and Zoledronate) study, a home-based randomized controlled trial to test the efficacy of zoledronic acid to prevent fractures in people with PD. Dr. Tanner is also a dedicated educator. She has been fortunate to serve as mentor to talented students from many countries, who themselves are now leading researchers and educators worldwide.

Music Therapy/Music Medicine

Melita Belgrave, Ph.D., M.T.-B.C., Arizona State University

Melita Belgrave, Ph.D., M.T.-B.C., received her bachelor's degree in music therapy from Michigan State University. She also earned her master's degree in music therapy, a certification in aging studies, and a doctorate in music education with an emphasis in music therapy at Florida State University. Dr. Belgrave has worked as a music therapist in special education, mental health, rehabilitation, hospice, geriatric, and intergenerational settings throughout Texas, Florida, Kansas, and Missouri. Her research interests are music therapy with older adults and intergenerational programming. She has presented at regional, national, and international conferences, and her research has been published in national and international journals including the *Journal of Music Therapy, Music Therapy Perspectives, Frontiers in Medicine,* and *Journal of Music Teacher Education*. She coauthored the text *Music Therapy and Geriatric Populations: A Handbook for Practicing Music Therapists*. Her current service includes working as the chair of the Diversity, Equity, and Inclusion Committee for the American Music Therapy Association. Additionally, Dr. Belgrave serves as a member of the editorial board for *Music Therapy Perspectives* and was the 2016–2018 chair of the International Seminar of the Commission on Special Music Education and Music Therapy. Prior to her appointment at Arizona State University (ASU), Dr. Belgrave taught in the music therapy program at the University of Missouri–Kansas City as an assistant and associate professor. At ASU, she teaches undergraduate and graduate music therapy courses, serves as the advisor for the music therapy student organization, and has been appointed as the administrator of the Arizona State University Music Therapy Clinic. Dr. Belgrave has also been appointed as a research affiliate at the Mayo Clinic in Arizona and conducts creative aging music groups in the community. In 2018 she was recognized by the Black Music Therapy Network with the annual service award in recognition for her exemplary commitment to advanced knowledge and practice in the field of music therapy. Additionally, Dr. Belgrave has authored a chapter in and coedited the text for *Music Therapy in a Multicultural Context: A Handbook for Music Therapy Students and Professionals*.

Joke Bradt, Ph.D., M.T.-B.C., Drexel University

Joke Bradt, Ph.D., M.T.-B.C., is professor and program director of the Ph.D. in Creative Arts Therapies program at Drexel University and a board-certified music therapist. Her federally funded research is focused on the use of music therapy for chronic pain and symptom management. She currently is conducting two NIH-funded clinical trials: a multisite trial on music therapy for chronic pain management in people with advanced cancer and a study examining the impact of music therapy on opioid tapering in cancer survivors with chronic pain. As a research team member of Creative Forces: National Endowment for the Arts Military Healing Arts Network, she has investigated the impact of music therapy on clinical outcomes in service members with post-traumatic stress, traumatic brain injury, and other psychological health concerns. She is the lead author of several Cochrane systematic reviews on music interventions with medical patients, and she is editor-in-chief of the *Nordic Journal of Music Therapy*.

Julene K. Johnson, Ph.D., University of California, San Francisco

Julene K. Johnson, Ph.D., is a cognitive neuroscientist with an undergraduate degree in music. She is a professor in the University of California, San Francisco School of Nursing's Institute for Health and Aging and codirector of the new Sound Health Network. She has a long-standing interest in studying music and health in both healthy aging and people living with dementia. Her previous work investigated preserved music skills in Alzheimer's disease and understanding the relationship between brain and music recognition in various neurodegenerative diseases. In 2010, she was a Fulbright Scholar in Jyväskylä, Finland, where she studied how community choirs help promote well-being among older adults. Dr. Johnson recently completed a large cluster-randomized trial that examined the effects of a community choir on the health and well-being of racially/ethnically and socioeconomically diverse older adults.

Edward Roth, Ph.D., Western Michigan University

Edward (Ed) Roth, Ph.D., currently serves as professor and director of the music therapy program and director of the laboratory for Brain Research and Interdisciplinary Neurosciences (BRAIN), both at Western Michigan University. He combines his passions for music and neuroscience by studying the biology and clinical application of music improvisation toward social bonding, connectedness, and flow for people with issues related to mental health. His publications appear in journals including *Frontiers in Human Neuroscience*, *Journal of Music Therapy, Nordic Journal of Music Therapy, Journal for the Professional Counselor, Perceptual and Motor Skills,* and Australian and Canadian journals of music therapy. As a music therapist, he worked in several clinical settings, including with clients diagnosed with various neurological, physical, and psychiatric disorders. He completed his clinical internship training in adult and adolescent psychiatry at the University of Michigan Medical Center (Ann Arbor, Michigan), and while a graduate student at Colorado State University, cofacilitated music therapy and counseling groups for adolescents from Columbine High School (Littleton, Colorado) diagnosed with post-traumatic stress and acute anxiety. His clinical work at Blythedale Children's Hospital (Westchester, New York) focused on children and teenagers with neurologic disorders, particularly traumatic brain injuries. Dr. Roth is a percussionist who primarily studied as a marimbist and more currently plays drums and piano.

Michael H. Thaut, Ph.D., University of Toronto

Michael H. Thaut, Ph.D., is currently a professor of music at the Rehabilitation Sciences Institute, University of Toronto. He also has cross-appointments in rehabilitation science and neuroscience. He also holds appointments as collaborator scientist at the Centre for Addiction and Mental Health Hospital Neuroimaging Division and the Li Ka Shing Knowledge Institute at St. Michael's Hospital, Toronto. He is director of the university's Music and Health Science Research Center and Music and Health Sciences graduate programs. His appointment is endowed by a Canada Research Chair Tier 1 award from the federal government of Canada. Dr. Thaut received his master's degree and Ph.D. in music from Michigan State University, with a cognate minor in movement science. He holds a special diploma in music from the Mozarteum University in Salzburg, Austria, and a German Diploma in Psychology/ Education from the University of Muenster. Prior to his appointment at the University of Toronto, he was a professor of music and professor of neuroscience as well as director of the School of the Arts at Colorado State University. He has held many visiting positions internationally including at the University of Michigan Department of Movement Science, Düsseldorf University Medical School, National Institute for Neuroscience Research IRCCS Santa Lucia/Rome, Heidelberg University of Applied Sciences, and Kurashiki Sakuyo Music

University in Japan. Dr. Thaut is an international leader in the basic and clinical neuroscience of music and has internationally recognized research in relation to the applications of auditory neuroscience, specifically for music and rhythm, to brain rehabilitation. He has more than 250 scientific publications and is the coeditor of the *Oxford Handbook of Music Psychology* and senior editor of the *Oxford Handbook of Music and Brain* and the *Oxford Handbook of Neurologic Music Therapy,* which was second in the annual British Medical Association book award in the category "Best New Book in Neurology 2015." He is president emeritus of the International Society for Clinical Neuromusicology, vice president of the International Society for Music and Medicine, vice chair for Special Study Sections at the World Federation for NeuroRehabilitation, and an Overseas Fellow of the Royal Society of Medicine, United Kingdom. His research team, in collaboration with medical science and clinician groups worldwide, developed the field of neurological music therapy, an evidence-based system of music-based interventions applied to neurorehabilitation practiced by certified clinicians in more than 50 countries and endorsed by the World Federation for NeuroRehabilitation. As a former professional violinist in the classical and folk genres, Dr. Thaut has recorded several albums and has toured throughout Europe extensively.

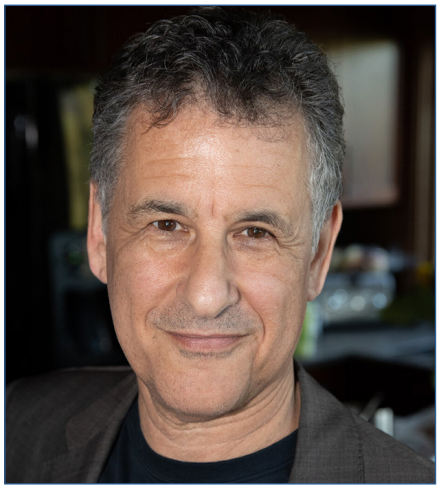
Neuroscience

John R. Iversen, Ph.D., University of California, San Diego

John R. Iversen, Ph.D., is a cognitive neuroscientist at the University of California, San Diego who studies the interactions between music and the brain. He directs the Studying the Influence Music Practice Has on Neurodevelopment in Youth (SIMPHONY) project and codirects the Early Academic Readiness and Learning Intervention (EARLI) project, part of a National Endowment for the Arts Research Laboratory. SIMPHONY and EARLI are longitudinal studies of the impact of music training on children's brain and cognitive development. They place the impact of music into a broader neurodevelopmental framework, in which researchers are charting the "growth curves" of the developing brain to understand how brain development shapes the emerging skills of each child. Dr. Iversen also studies fundamental brain mechanisms underlying human perception and production of sound and rhythm, mapping what they tell us about how the motor system may influence what we hear, as well as studies of biomarkers and brain mechanisms of navigation and complex skill learning. After undergraduate studies in physics at Harvard University, Dr. Iversen received graduate degrees in philosophy of science and in speech at the University of Cambridge and received a Ph.D. in speech and hearing science from the Massachusetts Institute of Technology. He is currently an associate research scientist in the Institute for Neural Computation and an associate director of the Swartz Center for Computational Neuroscience at the University of California, San Diego.

Nina Kraus, Ph.D., Northwestern University

Nina Kraus, Ph.D., is Hugh Knowles Professor of Communication Sciences, Neurobiology, and Otolaryngology at Northwestern University. She is a scientist, inventor, and amateur musician who studies the biology of auditory learning. As a biologist and musician, she thinks about sound and brain health. Observing single auditory neurons, she was one of the first to show that the hearing brain reorganizes itself when sound-to-meaning connections are made. These biological insights led her to investigate auditory learning in the human brain. Her research has found that our lives in sound, for better (musicians, bilinguals) and for worse (concussion, hearing loss, language disorders, noise), shape how our brain makes sense of the sounds we hear. Her book *OF SOUND MIND—How Our Brain Constructs a Meaningful Sonic World,* will be published by MIT Press this fall. Dr. Kraus advocates for biologically informed choices in education, health, and society.



Daniel J. Levitin, Ph.D., McGill University

Daniel J. Levitin, Ph.D., is a professor in the Department of Psychology at McGill University. He earned his B.A. in cognitive science from Stanford University and his M.Sc. and Ph.D. in cognitive psychology with a minor in music technology from the University of Oregon. He completed his postdoctoral training in neuroimaging and perception at the Stanford University School of Medicine and the University of California. He taught at Stanford University in the Departments of Computer Science, Psychology, History of Science, and Music and has been a visiting professor at Dartmouth College and the University of California, Berkeley. He is currently the founding dean of arts and humanities at the Minerva Schools at Keck Graduate Institute, San Francisco, California, and the James McGill Professor Emeritus of Psychology, Neuroscience, and Music at McGill University. Dr. Levitin is an award-winning neuroscientist, musician, and best-selling author. His research encompasses music, the brain, health, productivity, and creativity. Dr. Levitin has published more than 300 articles in periodicals such as *Science, Nature, Proceedings of the National Academy of Sciences, The New Yorker, The Atlantic,* and the *Wall Street Journal*. His research has been featured more than 1,800 times in the popular press, including 17 articles in *The New York Times* and in *The London Times, Scientific American,* and *Rolling Stone*. He is a frequent guest on National Public Radio and on CBC/Radio-Canada and has appeared on *Good Morning America, Today, CBS This Morning,* and CNN. His TED Talk is among the most popular of all time. He is the author of four *New York Times* bestselling books: *This Is Your Brain on Music, The World in Six Songs, The Organized Mind,* and *Successful Aging*, as well as the international bestseller *A Field Guide to Lies*. Dr. Levitin is a popular public speaker and has given presentations to Parliament in London, the U.S. Congress, Microsoft, Google, and Amazon.

He has consulted for a number of companies and organizations, including Apple, Booz Allen Hamilton, Microsoft, the U.S. Navy, Sonos, Philips, Sony, Fender, and AT&T. As a musician (tenor saxophone, guitar, vocals, and bass), he has performed with Mel Tormé, David Byrne, Rosanne Cash, Sting, Bobby McFerrin, Victor Wooten, and Tom Scott. Dr. Levitin has produced and consulted on albums by artists such as Stevie Wonder, Steely Dan, and Joni Mitchell, consulted on the films *Good Will Hunting* and *Pulp Fiction,* and has been awarded 17 gold and platinum records.

Psyche Loui, Ph.D., Northeastern University

Psyche Loui is associate professor of creativity and creative practice in the Department of Music at Northeastern University. She graduated from University of California, Berkeley with a Ph.D. in psychology, and from Duke University as an undergraduate with degrees in psychology and music. In the MIND (Music, Imaging, and Neural Dynamics) lab, Dr. Loui studies the neuroscience of music perception and cognition, tackling questions such as: What gives people the chills when they are moved by a piece of music? How does connectivity in the brain enable or disrupt music perception? Can music be used to help those with neurological and psychiatric disorders? Dr. Loui's work has received multiple Grammy awards, a young investigator award from the Positive Neuroscience Institute, and a career award from the National Science Foundation, and has been featured by the Associated Press, *The New York Times, The Boston Globe,* BBC, CNN, *The Scientist* magazine, and other news outlets.

Josh McDermott, Ph.D., Massachusetts Institute of Technology

Josh McDermott, Ph.D., is an associate professor, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology. He is a perceptual scientist studying sound, hearing, and music. His research addresses human and machine audition using tools from experimental psychology, engineering, and neuroscience. Dr. McDermott is particularly interested in using the gap between human and machine competence to both better understand biological hearing and design better algorithms to analyze sound and enhance human hearing.

Patient Advocacy and Arts Organizations

Barbara A. Else, M.P.A., M.T.-B.C., American Music Therapy Association

Barbara A. Else, M.P.A., M.T.-B.C., is a senior research and policy advisor with the American Music Therapy Association (AMTA). She coordinates AMTA's research initiatives and is the business manager for the AMTA's two peer-reviewed journals, the *Journal of Music Therapy* and *Music Therapy Perspectives*. She also serves as managing editor for the *Journal of Music Therapy*. Ms. Else practiced as a hospital-based music therapist and has been active as a researcher in health policy and economics. She maintains a part-time music therapy practice in community mental health. She provides training and presentations on the use of music therapy to mitigate the effects of trauma. Ms. Else was the recipient of a postgraduate fellowship and later served as a project officer with the U.S. Public Health Service at the Agency for Health Care Policy and Research (later renamed the Agency for Healthcare Research and Quality) for medical effectiveness research, policy analysis, and grants management. Her publication credits focus on health policy, research methods, trauma and music therapy, and health economics. Ms. Else volunteers with the American Red Cross in disaster services/mental health and training. She serves in an advisory role for disaster response for the AMTA and the World Federation of Music Therapy. As a musician, Ms. Else is active (in nonpandemic times) in the jazz scene and is a studio recording artist specializing in concert and ethnic flutes.

Rebecca Gilbert, Ph.D., M.D., American Parkinson Disease Association

Rebecca Gilbert, Ph.D., M.D., joined the American Parkinson Disease Association (APDA) in 2018 as chief scientific officer and is responsible for overseeing APDA's research portfolio in conjunction with APDA's Scientific Advisory Board. Dr. Gilbert provides medical and clinical expertise to support APDA programming as well as print and web content. Dr. Gilbert received her M.D. degree at Weill Medical College of Cornell University and her Ph.D. in cell biology and genetics at the Weill Graduate School of Medical Sciences. She then completed her neurology residency training as well as movement disorders fellowship training at Columbia Presbyterian Medical Center. Dr. Gilbert continues to maintain a limited schedule of patients one day a week through Bellevue Hospital Center. Prior to joining APDA, she was an associate professor of neurology at the Fresco Institute for Parkinson's and Movement Disorders, NYU Langone Medical Center where she saw movement disorders patients at both NYU and Bellevue Hospital Center, initiated and directed the NYU Movement Disorders Fellowship, participated in clinical trials and other research initiatives for Parkinson's disease, and lectured widely on Parkinson's disease.

Anne Leonard, M.P.H., B.S.N., R.N., American Stroke Association/American Heart Association

Anne Leonard, M.P.H., B.S.N., R.N., is a senior science and medicine advisor for the American Stroke Association (ASA) division of the American Heart Association (AHA). She is the lead for the Stroke Council, Council on Hypertension, and Council on Clinical Cardiology and staffs several science subcommittees within those councils. She has worked in stroke science since 1987, when she worked for the Department of Neurology at the University of Texas Health Science Center at San Antonio on the Stroke Prevention in Atrial Fibrillation study, which was funded by the National Institute of Neurological Disorders and Stroke. During her 20-year tenure with this department, she also coordinated other studies on acute stroke treatment, primary/secondary prevention of stroke, and novel early-phase neuroprotective agents. Her work on these research studies included the roles of study coordinator and sub investigator. She also was involved in quality improvement projects at affiliated hospitals. She worked 5 years of her career with the Department of Neurosurgery, coordinating and executing clinical research trials on intracerebral hemorrhage, including two surgical intervention studies (the Minimally Invasive Surgery and rtPA for Intracerebral Hemorrhage Evacuation study and the Clinical Trial on Treatment of Intraventricular Hemorrhage), as well as an epidemiology study (Ethnic/Racial Variations of Intracerebral Hemorrhage). She served as the interim stroke coordinator in the five-hospital system for a year and consulted with this system thereafter. During those years, she taught residents, medical students, nurses, paramedics, and allied health professionals about stroke. Before leaving the university, she consulted with the AHA/ASA about its stroke portfolio. She rejoined the AHA/ASA in 2013.

Sunil Iyengar, National Endowment for the Arts

Sunil Iyengar is director of the Office of Research & Analysis at the National Endowment for the Arts (NEA). Under his leadership, the office has produced dozens of research reports, hosted periodic research events and webinars, led strategic plan development for the agency, and established research and data partnerships with the U.S. Census Bureau and the Bureau of Economic Analysis. His office also conducts program evaluations and performance measurement for the Arts Endowment. Working with his team, Mr. Iyengar has created and pursued a long-term research agenda (based partly on an arts "system map" his office helped to design), founded a national data repository for the arts, and launched two awards programs for arts researchers, including the NEA Research Labs initiative. He chairs a Federal Interagency Task Force on the Arts and Human Development. For nearly a decade, he has contributed a monthly research post ("Taking Note") to the agency's official blog. Mr. Iyengar and his team have collaborated with organizations such as the Brookings Institution, the National

Academy of Sciences, the Robert Wood Johnson Foundation, the Association of American Medical Colleges, and NIH to explore the arts in relation to such topics as health and well-being, economic development, and STEM (science, technology, engineering, and mathematics) and medicine. His office provides research consultative support to Creative Forces: NEA Military Healing Arts Network. Most recently, he has led a research funding partnership with NIH as part of Sound Health. His office supports the Sound Health Network. Prior to joining the agency, Mr. Iyengar worked as a reporter, managing editor, and senior editor for news publications covering the biomedical research, medical device, and pharmaceutical industries. He writes poems, book reviews, and literary essays. Mr. Iyengar has a B.A. in English from the University of Michigan.

Susan Magsamen, M.A.S., Johns Hopkins University

Susan Magsamen, M.A.S., received a bachelor's degree in communications studies from Towson University in 1982 and a master's degree in advanced study from Johns Hopkins University in 1986. She is the founder and executive director of the International Arts + Mind (IAM) Lab, a pioneering neuroaesthetics initiative from the Pedersen Brain Science Institute at Johns Hopkins University School of Medicine. Her body of work lies at the intersection of brain sciences and the arts—and how our unique response to aesthetic experiences can amplify human potential. Ms. Magsamen is the author of the Impact Thinking model, an evidence-based research approach to accelerate how we use the arts to solve problems in health, well-being, and learning. In addition to her role at the IAM Lab, she also serves as codirector of the NeuroArts Blueprint initiative in partnership with the Aspen Institute. Prior to founding the IAM Lab, Ms. Magsamen worked in both the private and public sectors, developing social impact programs and products addressing all stages of life—from early childhood to aging adulthood. She created Curiosityville, an online personalized learning world, acquired by Houghton Mifflin Harcourt in 2014, and Curiosity Kits, a hands-on multisensory company, acquired by Torstar in 1995. Ms. Magsamen, an award-winning author for children and families, has published seven books, including *The Classic Treasury of Childhood Wonder, The 10 Best of Everything Families,* and *Family Stories,* a five-part interactive series that included *Nighty Night, Tooth Fairy Times, My Two Homes, Family Night,* and *Making Spirits Bright*. She is a fellow at the Royal Society of the Arts and a strategic advisor to several innovative organizations and initiatives, including the Academy of Neuroscience for Architecture, the American Psychological Association, the National Association for the Education of Young Children, Brain Futures, Learning Landscapes, and Creating Healthy Communities: Arts + Public Health in America.

Bruce Miller, M.D., University of California, San Francisco

Bruce Miller, M.D., holds the A.W. and Mary Margaret Clausen Distinguished Professorship in Neurology at the University of California, San Francisco, where he directs the Memory and Aging Center. As a behavioral neurologist whose work emphasizes brain-behavior relationships, he has reported on the emergence of artistic ability, personality, cognition, and emotion with the onset of neurodegenerative disease. Dr. Miller is the principal investigator of the NIH-sponsored Alzheimer's Disease Research Center and program project on frontotemporal dementia. Also, Dr. Miller helps lead the Tau Consortium, the Bluefield Project to Cure Frontotemporal Dementia, and the Global Brain Health Institute. Dr. Miller was awarded the Potamkin Award from the American Academy of Neurology and elected to the National Academy of Medicine.

Group Abstracts

Behavioral and Social Science Intervention Development

Group Members:

Bryan Denny, Ph.D., Rice University

Sona Dimidjian, Ph.D., Renée Crown Wellness Institute and University of Colorado Boulder

Eric Garland, Ph.D., LCSW, University of Utah

Assal Habibi, Ph.D., University of Southern California

Susan Landau, Ph.D., University of California, Berkeley

Music-based interventions (MBIs) have the potential to manage symptoms, slow disease progression, rehabilitate, and improve quality of life for persons with Alzheimer's disease and Alzheimer's disease–related dementias (AD/ADRD), Parkinson's disease (PD), and stroke. For MBIs in these populations, we discussed 1) important considerations for selecting biomarkers, 2) what types of biomarkers could be linked to clinical outcomes, and 3) potential biomarker candidates associated with biological effects and clinical benefits.

1. An important consideration in the selection of biomarkers for MBIs in AD/ADRD, PD, and stroke is that MBIs, disease outcomes, and the populations of interest are all heterogeneous. Further, nondrug interventions may be more likely to offer protection against worsening symptoms rather than alter the underlying disease itself. Thus, disease-defining biomarkers (e.g., amyloid and tau accumulation for AD, loss of dopaminergic function in PD) may play a greater role in characterizing the severity of neurodegenerative disease at baseline or predicting who could benefit most from MBIs rather than as outcomes modified by MBIs. Cognitive decline, quality of life, and social/emotional regulation are examples of outcomes that could be modified by MBIs via changes in reserve or resilience mechanisms across all populations. It is important to consider the link between the nature of the intervention and the specific processes affected.

   Relatedly, future MBI research may benefit from attempting to disentangle the specific cognitive, social/emotional, and/or sensory processes targeted that may be driving clinical benefits of the MBI, as per the NIH Science of Behavior Change (SOBC) framework. The general consensus from research on the biological basis of change as a result of MBIs is that the systems directly influenced by music, such as the auditory and motor systems (e.g., as assessed via structural volume or connectivity of the auditory cortex) and the reward system (e.g., assessed by functional magnetic resonance imaging and raclopride positron emission tomography), may be most likely to show target engagement. However, if future MBIs include increasingly tightly matched and

hypothesis-driven music-based control interventions, it may be possible to disentangle which processes or systems are driving which clinical benefits to what extent and over what timescale, which could spur specification of increasingly sensitive and specific clinically relevant biomarkers. In so doing, this approach would further elucidate the "active ingredients" of different MBIs. Models for such dismantling or additive designs with other nonpharmacologic approaches exist, for example, in research on cognitive behavioral and mindfulness-based therapies for other disorders. In investigating such mechanisms, it will be important to consider how MBIs may be affecting certain systems or processes initially (e.g., initial auditory perception changes) in ways that could have later downstream effects on other processes (e.g., subsequent cognitive, social, or emotional benefits). An additional related, important consideration pertains to the nature of the MBI. Music learning interventions (i.e., learning to play an instrument) are likely to have distinct targets, mechanisms of action, and consequently best-fit biomarkers in comparison to more passive MBIs (e.g., listening to music).

2. Following from the SOBC framework, the types of biomarkers needed for predictive and prognostic purposes (e.g., to identify who is more or less likely to be responsive to the intervention) may be different than biomarkers best suited to assess changes in disease progression or changes in clinical outcomes overall.

3. When considering potential biomarkers, it is important to highlight that each targeted population (i.e., persons with AD/ADRD, PD, and stroke) entails unique pathophysiological mechanisms, and MBIs for particular populations would target unique clinical outcomes. Thus, disease-defining biomarkers may be distinct from biomarkers related to the particular MBI and the processes/systems it is targeting. Machine learning methods to examine whether there are particular neural signatures that are specific to undergoing different types of MBIs that are in turn related to different clinical benefits (e.g., using patterns of resting state functional connectivity or other functional neuroimaging-based measures) may be useful.

Clinical Trials Methodology

Group Members:

Roger Fillingim, Ph.D., University of Florida

Ken Freedland, Ph.D., Washington University in St. Louis

Sheri Robb, Ph.D., M.T.-B.C., Indiana University

Caroline Tanner, M.D., Ph.D., University of California, San Francisco

Brain disorders of aging (e.g., Alzheimer's disease and Alzheimer's disease–related dementias [AD/ADRD], Parkinson's disease [PD], and stroke) are complex conditions impacting numerous biological, behavioral, and cognitive-affective systems; therefore, multiple factors merit consideration in selection of biomarkers for music interventions targeting these disorders. Practical factors are important, including cost, resource requirements (e.g., expertise, equipment), and participant burden, and must be considered

in light of the research context, for example a multicenter pragmatic trial conducted in clinical settings versus a single-site mechanistic trial performed in a specialized academic center. Another important practical consideration is the temporal resolution of the biomarker, as changes in some biological responses (e.g., brain structure, epigenetic changes) may emerge too gradually to be detected in the time course of a typical clinical trial. Biomarker selection will also be strongly influenced by the question(s) being addressed in the clinical trial. Indeed, biomarkers serve multiple purposes, raising additional considerations in biomarker selection. For example, if a biomarker is being used as a surrogate or intermediate outcome, the biomarker must: 1) have a strong relationship to the clinical outcome of interest, 2) be potentially modifiable by the intervention, and 3) be sensitive to change. Biomarkers may also be useful in determining whether the intervention is engaging the target. In the context of music, this could involve assessment of biological or sensory responses to ensure that music is engaging the systems (e.g., sensory, cognitive) required to exert a therapeutic effect. This may dictate use of such biomarkers during prescreening or even in a pilot project to ensure appropriate target engagement. While biomarkers can be useful for this purpose, it is important to recognize that self-report or observational data can often be more effective in assessing whether music is having the intended effect, particularly given the wide interindividual variability in responses to music. Biomarkers may also be useful for interventional phenotyping, in which an individual's biological response to an acute episode of the intervention can be used as a potential predictor of future therapeutic response to a full dose of the intervention. However, if a project intends to identify mediators of response to an intervention, it is critical that this be incorporated into the trial design a priori, as post hoc efforts are often underpowered due to insufficient variability in the mediator.

Given these considerations and the multiple systems impacted by brain disorders of aging, numerous potential biomarkers exist. In selecting biomarkers for clinical trials, it is important to recognize that music could affect a clinical outcome through a mechanism that is independent of the pathophysiology of the disease, and both disease-specific and outcome-specific mechanisms should be considered in biomarker selection. One such example might be inflammation, which is not considered a primary disease mechanism but can influence disease progression and may be responsive to interventions. While diagnostic markers may be useful for observational or mechanistic studies, their utility in the context of clinical trials is limited. Moreover, music interventions may have broader impacts on biological and behavioral outcomes compared to more typical interventions such as medications, which may dictate a need for different types of biomarkers in music trials. Potential biomarkers for music interventions in brain disorders of aging include: multiple neuroimaging and electroencephalographic markers of brain structure and function (e.g. receptor occupancy, functional magnetic resonance imaging), sensor-based motor and behavioral measures (e.g. body sway, mobility), markers of autonomic function, measures of motor function, markers extracted from biological samples (e.g., cerebrospinal fluid, blood, saliva), biometric measures, genetic/epigenetic markers, and objective measures of affective processes (e.g., tone of voice, facial expression). Another question impacting biomarker selection is the extent to which the markers must directly reflect a biological process. For example, sensory tests or responses assessed by wearable sensors might be considered biomarkers, even though the response measures are not directly biological. In summary, multiple factors must

be considered when selecting biomarkers, including practical and scientific concerns. Nonetheless, there remain many viable candidate biomarkers for assessing responses to music interventions in brain disorders of aging.

Music Therapy/Music Medicine

Group Members:

Melita Belgrave, Ph.D., MT-BC (not present), Arizona State University

Joke Bradt, Ph.D., MT-BC, Drexel University

Julene K. Johnson, Ph.D., University of California, San Francisco

Edward A. Roth, Ph.D., MT-BC, Western Michigan University

Michael H. Thaut, Ph.D., University of Toronto

1. **What are important considerations for selecting biomarkers for Alzheimer's disease and Alzheimer's disease–related dementias (AD/ADRD), Parkinson's disease (PD), and stroke?**

    a. Behavioral issues such as agitation, frustration, and/or high levels of anxiety may make data collection of biomarkers difficult among people with mid-to-late stage dementias (e.g., functional magnetic resonance imaging [fMRI] or blood draws).

        i. Participants with mild cognitive impairment are more motivated than patients with late-stage AD. Participants need to be early enough in the stages of disease to cooperate with the procedures but late enough to get meaningful data from the biomarkers.

    b. Typical funding amounts may not cover the costs of a sufficiently powered study (given the costs related to fMRI, for example), and our recommendations should include this consideration.

        i. Neurotransmission imaging was discussed, and it was pointed out that although this technique is highly useful, there are only a few places in the world that have this capability, and it is roughly four times the cost of typical fMRI.

    c. Gene expression obtained from saliva or blood is easier to collect than fMRI task-dependent brain imaging.

    d. Double-density electroencephalogram (EEG) may be appropriate, as 256 electrodes give much better spatial resolution than traditional EEG applications, and the temporal acuity would be better than fMRI.

    e. Studies would need to include personnel with expertise related to specific biomarkers.

    f. Criteria for rigor: observer and implementer blinding; reproducibility.

        i. The need for dose matching (time, intensity, and constructs) between experimental and control conditions.

g. Whether the biomarkers are intended to measure neuroprotectivity or connectivity.

h. How well correlated the biomarkers are to behavioral or self-report outcomes.

i. Important to take into account the diurnal rhythm for certain biomarkers, such as cortisol.

j. Timeframe of the effects. An intervention could generate an effect immediately identifiable by a biomarker, or an intervention could generate a positive, long-term effect that might be identified by a different biomarker at the end of a 6- to 8-week study.

k. Levels of intervention needed to generate clinical outcomes.

l. Imaging studies need to have clear behavioral hypotheses. Proof of principle improves the likelihood of funding.

2. **What types of biomarkers could be linked to clinical outcomes in music-based interventions for AD/ADRD, PD, and stroke?**

   a. Changes in neurochemistry.

      i. Cortisol or adrenocorticotropic hormone (ACTH) linked to changes in anxiety/agitation.

      ii. Brain derived neurotrophic factor (BDNF) as a possible measure for neuroplasticity.

   b. Dopamine (for PD).

      i. Consider neurotransmission imaging.

      ii. Collection from tears is thought to be a better measure of central dopamine than peripheral dopamine circulating in the blood.

3. **In music-based intervention protocols, can we identify markers that are associated with biological effects and clinical benefits?**

   a. Markers of gene expression or brain response that identify neuroplasticity.

      i. Improved voice control, tone of voice, or vocal quality resulting from singing (related to PD).

   b. Social engagement.

      i. Oxytocin, eye contact, synchronization of body sway across participants, motion capture.

   c. Intracellular responses from a surgical implant for gait disorders related to PD.

Neuroscience

Group members:

John Iversen, Ph.D., University of California, San Diego

Nina Kraus, Ph.D., Northwestern University

Daniel Levitin, Ph.D., McGill University

Psyche Loui, Ph.D., Northeastern University

Josh McDermott, Ph.D., Massachusetts Institute of Technology

Musical experiences have been shown to engage multiple brain networks involved in domains including sensory processing, movement, language, attention and memory, emotion and reward, and social connectedness. As such, there is a wide range of potential biomarkers that have the potential not only to assess disease conditions and effectiveness of interventions, but also to give fundamental insight into brain mechanisms. Some of these biomarkers are relevant for any study of aging, regardless of underlying disorder, as they concern universal, fundamental abilities, including sensory processing and emotion and social connectedness, with which music interacts.

Sensory processing: As music deals fundamentally with sound, one important ability to consider is hearing in noise. Older adults experience difficulties with hearing in noise, which can lead to difficulties in everyday communication and consequent isolation. As such, a useful biomarker for auditory function comes from electroencephalography (EEG), specifically the auditory frequency-following response (FFR). There is a need to develop better measures to test hearing in noise in realistic situations.

Emotion and social connectedness: Beyond sensory processing, music affects emotion and social connectedness, which in turn affect mood, cognition, and perception. Thus, studies on music-based interventions (MBIs) should consider the general impacts of music on social and emotional domains, as well as disease-specific effects of MBIs. For understanding emotion and reward, neuroimaging offers some useful biomarkers, such as structural and functional neuroimaging of the dopaminergic reward system and structural and functional connectivity between auditory and reward systems. Psychophysiological biomarkers such as galvanic skin response and pupil diameter, while complex to work with, may be additionally useful as indices of arousal. For each of these tools, studies may look at changes over time in a person's response, effectively using within-subject designs in which study participants may be able to serve as their own controls.

Individual choice: MBIs that allow for individual differences in choice of music are more likely to work than ones that dictate or prescribe specific music. Thus, a toolkit of biomarkers for MBIs needs to be adaptable toward individual as well as cultural differences in musical experience. Neuroscientists should work with music therapists to record and analyze brain data in ways that respect these cultural and individual variations.

Rhythm and movement: Rhythm is a universal feature of music that may have implications for wellness across multiple diseases, particularly Parkinson's disease (PD) and stroke.

Specifically, biomarkers that show the effect of rhythm, such as EEG and gait or movement measures, are important for MBIs on PD such as rhythmic auditory stimulation (RAS). Rhythm is also important for attention, perception, memory, and turn-taking. The latter is one of the therapeutic targets for MBIs such as melodic intonation therapy (MIT) for recovering from aphasia after stroke. In working with stroke patients, a predictive behavioral biomarker may include the ability to sing, which predicts whether the person will respond well to MIT. Neuroimaging of the auditory-motor pathways, including structural neuroimaging of white matter pathways such as the arcuate fasciculus, and dynamic connectivity assessed using functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), or EEG, provides potentially effective biomarkers for MIT, RAS, and novel rhythmic interventions, thus benefiting patients with stroke and with PD.

Memory: Memory is an important target domain for MBIs, especially for Alzheimer's disease (AD) and related disorders. Although therapeutic effects on cognition are variable across individuals, music therapists have long been engaging memories for those with AD using familiar songs. A person with AD who has poor memory for faces and names may nevertheless remember a song that was personally important to them; in this way, music offers a portal for communication that can impact both the patient, and, crucially, the caregivers. Cognitive science may be especially useful in conceptualizing memory, for example in terms of episodic versus semantic memory. In AD, while people lose episodic memory, semantic memory may remain relatively intact. For these individuals, practical memory measures such as activities of daily living may carry the most clinical significance and be useful for the toolkit.

To conclude, in addition to disease-specific biomarkers, we suggest the inclusion of common measures across disorders in the toolkit, including basic auditory perception and emotional and social response measures. Diagnostic and predictive biomarkers also of more specific disease-related mechanisms may include electrophysiological indices, gray matter structure and white matter pathways, functional and neurotransmitter imaging, gold-standard neuropsychological measures, sensitivity to music and reward (e.g., Barcelona Music Reward Questionnaire), and general measures of musical experience and training (e.g., Goldsmith Music Sophistication Index) to provide contextual factors that may be needed to parse individual differences in response to music-based interventions. In the future, neural biomarkers may be useful in mechanistically understanding individual differences in responsiveness to MBIs for a variety of disorders.

Patient Advocacy and Arts-Based Organizations

Group Members:

Barbara Else, M.P.A., M.T.-B.C., American Music Therapy Association

Rebecca Gilbert, M.D., Ph.D., American Parkinson Disease Association

Sunil Iyengar, National Endowment for the Arts

Anne Leonard, M.P.H., B.S.N., R.N., American Stroke Association/American Heart Association

Susan Magsamen, M.A.S., Johns Hopkins University

Bruce Miller, M.D., University of California, San Francisco

Abbreviated discussion question: Music-based interventions (MBIs) have the potential to… what are important considerations for selecting biomarkers for Alzheimer's disease and Alzheimer's disease–related dementias (AD/ADRD), Parkinson's disease (PD), and stroke?

The panel discussed this question in detail from the perspective of patient advocates and arts-based organizations. The group generated a series of recommendations surrounding the types of interventions, the type and stage of disease, the best symptoms to target, and the most efficacious biomarkers to measure for different disorders, noted above.

Part 1: Whom to target:

1. **What should be targeted with MBIs—quality of life, slowing progression, and/or symptom management?** There was enthusiasm among panelists for considering symptom management and quality of life for AD/ADRD and PD. Slowing disease progression for these conditions was considered a "high bar" and harder to achieve, given widespread structural and functional change in the brain by the time of diagnosis. Music training earlier in life produces positive structural changes in white matter, and this could have long-term protection throughout life. The effect of early-life music interventions should be considered in studies. Stroke seemed to offer different opportunities and challenges, and a therapeutic trial following stroke should consider quality of life, symptom management, and disease outcomes. The case of former Representative Gabby Giffords was referenced.

2. **What stage of disease should be targeted?** Panelists focused upon mid-to-early stages of disease. Participation and engagement in MBIs can be increasingly difficult as AD/ADRD and PD advance, i.e., regarding attention, fatigue, and cooperation. Advocates encourage work in all stages, but investment in early and mid-stages may yield downstream patient benefits. The same is true for vascular dementia or massive strokes. Also, with mild disease it is more likely that there will be homogeneity in symptoms and participation. Treating a relatively homogeneous population with regard to age, disease, and disease severity with a control intervention was recommended. Music literacy is another factor that needs to be considered. With regard to obtaining a homogeneous population following stroke, controlling for infarction size, lateralization, localization (insula, hippocampus, prefrontal, basal ganglia, thalamus, motor or sensory strip, etc.) and premorbid music skills will be important factors if a trial is going to be successful.

Part 2: What domains should be targeted?

1. For ADRD and PD, there are scales that capture global cognition and global function, like the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery and the NIH Toolkit. Similarly, specific cognitive domains can be captured for memory (California Verbal Learning Test, TABCAT) and executive function, such as the NIH-Examiner, which has multiple forms and can be easily adapted to a clinical trial design. While improvement in a specific musical task is

of value by itself, transfer of treatment effects into broader functional and cognitive measures is desired. Use of traditional paradigms that have already gone through an approval process (like CERAD) will be valuable for any trial that seeks approval for a music method through the U.S. Food and Drug Administration. Another idea discussed was the use of health economic and costs analyses around patient and caregiver burden that may prove to further validate an MBI if cost savings are identified.

Panelists discussed the value of targeting other domains including mood, anxiety, emotion, speech, and movement in the case of PD, all of which might be strongly influenced by an MBI. Many panelists consider psychopathology and emotion as outcomes equal in importance to traditional measures of cognition. Depression, irritability, and anxiety are common features of AD, dementia with Lewy bodies, and frontotemporal dementia (FTD), and these symptoms increase the burden for both the patient and the caregiver. These symptoms are feasible targets for singing or dance interventions with music. There are a variety of scales available to test global psychopathology, like the Neuropsychiatric Inventory (NPI or NPI-Q), that have been validated and adapted to the study of dementia. Typically, the NPI is scored by the caregiver. Also, there are excellent scales of mood like the global depression scale and the Beck depression inventory that are self-scored. The Cornell scale for depression in dementia is scored by the clinician based upon interviews with the patient and family. While the depression and global scales capture many features of anxiety, the Rating Anxiety in Dementia (RAID) scale is another reliable and valid scale that could be used.

Emotion regulation is altered in different ways with different dementias, and new quantitative laboratory-based measures are available that use specific paradigms that measure perception, autonomic regulation (heart rate, skin response, respiration), and facial movement. Showing changes in autonomic tone longitudinally, such as increasing heart rate variability, and tying this to self- and caregiver-administered or self-administered scales of emotional well-being, could bring a novel, efficient, and effective way to show the value of MBIs in dementia.

Finally, excellent measures of movement pioneered by the movement disorders community may be useful. The gold-scale for movement in PD is the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Other scales are available for vocalization, gait, and tremor.

2. **Assessing the Caregiver:** Panelists emphasized the value of dual assessment of both the patient and the caregiver with any intervention. Often, caregiving increases stress and exacerbates psychological and physical problems. Factors in the patient that increase burden for caregivers include apathy, aggression, and diminished empathy. Depression and anxiety are common for caregivers, and many even attribute physical illnesses to the caregiving process. The Symptom Checklist 90-Revised (SCL-90-R) is a 90-item questionnaire assessing nine domains of psychopathology in the past week. It can be filled out by both caregivers and patients. Global health can also be assessed in caregivers and partners using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). The SF-36 evaluates eight areas of mental and physical health.

3. **MBIs:** A variety of MBIs were discussed. COVID-19 has taught us that people can participate in a study online rather than through in-person sessions, increasing the ease with which participants can access music therapy and MBIs. While the group did not consider individualized therapies for musicians who suffer a brain injury, the example of Gabby Giffords was mentioned, and the use of a previously learned music skillset could be studied as an outcome by itself. Often, in addition to music therapy as one of the treatments, it is also used as an adjunct to other approaches that support patient readiness for treatment, may improve recovery progress (i.e., in PD), and make treatment outcomes better. In dementia, the MIDDEL (Music Interventions for Dementia and Depression in Elderly Care) is a multinational pragmatic cluster-randomized trial to determine the effectiveness of two music interventions (group music therapy, recreational choir singing) for reducing depression symptoms in people living with dementia, and to examine mechanisms and heterogeneity of treatment effects.

   A wide variety of MBIs have been studied, including individual and group MT protocols and techniques as well as melodic intonation therapy and use of rhythm in speech and language. Music with dance movement has been employed in elders with and without dementia. Entrainment is defined in Wikipedia as "a temporal locking process in which one system's motion or signal frequency entrains the frequency of another system" (Thaut et al., 2015, Wikipedia). Entrainment may be especially useful in MBIs with PD patients. One study found that participants reported increased mobility in connection with their increased dancing. Dance or song for PD patients, therefore, could be considered low-hanging fruit.

   The Music on Our Minds study, which looked at stroke, is a useful reference for this topic. Positive changes are seen with music therapy but the exact mechanisms for these changes are less known. Further, little is known about the ways in which music therapy affects patients during the critical first 90 days of rehabilitation. Beneficial effects are seen, but it's unclear whether they are due to changes in motivation or changes in outcomes. Following acute stroke, depression is common and would be a potential target for therapy.

Part 3: What biomarkers may be most effective in detecting positive change?

1. **Blood biomarkers:** Both patients and caregivers experience stress. Blood biomarkers including adrenocorticotropic hormone (ACTH), noradrenaline, cortisol, and leptin rise with increasing stress. Some work suggests that a positive music intervention influences these biomarkers in a positive direction (Koelsch, 2016), although further work is needed, particularly to determine the value of MBIs in dementia. Similarly, stress affects the immune system, and proinflammatory cytokines such as IL-6 and TNF-alpha can rise during stress. Some work suggests that elevation of these proinflammatory cytokines is a feature of specific forms of FTD. Another blood biomarker that could be considered is neurofilament light chain (NFL-1), which is released from axons with many neurodegenerative conditions (FTD and amyotrophic lateral sclerosis [ALS] > AD > PD) (Rojas, 2021). There are emerging blood biomarkers that can detect amyloid-b42 and phosphorylated tau in the blood. The diagnostic accuracy for these markers is

approaching that of positron emission tomography (PET) imaging. Cerebrospinal fluid (CSF) biomarkers for amyloid and tau are also very good but likely too invasive for a field-based MBI.

2. **Neuroimaging:** Neuroimaging is being used to ascertain a diagnosis. It is hard to imagine a clinical trial in AD that would not require at least amyloid and probably tau PET. Magnetic resonance imaging (MRI) is being used in clinical trials to assess longitudinal change in all the dementias, and MRI has been standardized for studies that approach disease modification in AD, PD, and FTD. Structural MRI might not be as valuable to study longitudinal change, but functional MRI could be used to determine whether specific circuits have been activated by MBIs in music therapy.

Panelists' Questions

1. Music-based interventions have the potential to manage symptoms, slow disease progression, rehabilitate, and improve quality of life. Knowing that important domains of brain disorders of aging are emotion, cognition, and motor and sensory function, what are important considerations for selecting biomarkers for Alzheimer's disease and Alzheimer's disease–related dementias, Parkinson's disease, and stroke?
2. What types of biomarkers (predictive, prognostic, diagnostic, disease progression, treatment response) could be linked to clinical outcomes in music-based interventions for Alzheimer's disease and Alzheimer's disease–related dementias, Parkinson's disease, and stroke?
3. In music-based intervention protocols, can we identify markers that are associated with biological effects and clinical benefits?

NIH Planning Committee

Caitlin Burgdorf, Ph.D., Office of Behavioral and Social Sciences Research

Tom Cheever, Ph.D., National Institute of Neurological Disorders and Stroke

Wen Chen, Ph.D., National Center for Complementary and Integrative Health

Emmeline Edwards, Ph.D., National Center for Complementary and Integrative Health

Robert Finkelstein, Ph.D., National Institute of Neurological Disorders and Stroke

David Frankowski, Ph.D., National Institute on Aging

Dana Greene, Ph.D., Office of Behavioral and Social Sciences Research

Lisa Onken, Ph.D., National Institute on Aging

Amy Poremba, Ph.D., National Institute on Deafness and Other Communication Disorders

Robert Riddle, Ph.D., National Institute of Neurological Disorders and Stroke

Coryse St. Hillaire-Clarke, Ph.D., National Institute on Aging

Nena Wells, National Center for Complementary and Integrative Health

Suggested Reading List

Experimental Design

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- Community of Voices research study: A research study (2012–2018) using a cluster-randomized clinical trial design examined whether singing in a community choir could promote health and well-being among culturally diverse older adults. The Community of Voices choir program comprised weekly choir sessions for 12 months. Sessions were held at senior centers throughout San Francisco, and professional choir directors led the sessions.

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Suggested Resources

Barcelona Music Reward Questionnaire (BMRQ): A questionnaire that assesses the musical reward experience, decomposed into five reliable factors: Musical Seeking, Emotion Evocation, Mood Regulation, Social Reward, and Sensory-Motor.

California Verbal Learning Test (CVLT): An assessment of verbal learning and memory for older adolescents and adults. In the CVLT, an examinee listens to series of words and is then asked to recall the terms and the category to which they belong.

Computerized Adaptive Testing for Mental Health Disorders (CAT-MH™): A suite of measures validated for depression, anxiety, mania/hypomania, substance use disorder, psychosis, post-traumatic stress disorder, social determinants of health, adult attention-deficit hyperactivity disorder, and suicidality.

The Goldsmiths Musical Sophistication Index (Gold-MSI): A self-report inventory for individual differences in musical sophistication. It measures the ability to engage with music in a flexible, effective, and nuanced way.

Medical Outcomes Study 36-Item Short Form Health Survey (SF-36): A set of generic, coherent, and easily administered quality-of-life measures. These measures rely upon patient self-reporting and are now widely utilized by managed care organizations and by Medicare for routine monitoring and assessment of care outcomes in adult patients.

Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS): A scale developed to evaluate various aspects of Parkinson's disease including nonmotor and motor experiences of daily living and motor complications. It includes a motor evaluation and characterizes the extent and burden of disease across various populations.

Music in Dementia Assessment Scales (MiDAS): Scales developed to measure observable musical engagement of persons with moderate or advanced dementia who may have limited verbal skills to directly communicate their musical experiences.

Music Interventions for Dementia and Depression in Elderly Care (MIDDEL): A multinational pragmatic cluster-randomized trial to determine the effectiveness of two music interventions (group music therapy, recreational choir singing) for reducing depression symptoms in people living with dementia, and to examine mechanisms and heterogeneity of treatment effects.

Neuro-QoL (Quality of Life in Neurological Disorders): A measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults and children living with neurological conditions.

Neuropsychiatric Inventory (NPI): A measure to assess dementia-related behavioral symptoms that the developers felt other measures did not sufficiently address. The NPI originally examined 10 subdomains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability,

and aberrant motor activity. Two more subdomains have been added since its development: nighttime behavioral disturbances and appetite and eating abnormalities. This wide variety of domains means that, unlike other dementia measures, the NPI can screen for multiple types of dementia, not just Alzheimer's disease.

NIH EXAMINER: A neuropsychological test battery to reliably and validly assess domains of executive function (often defined as the ability to engage in goal-oriented behavior) for clinical investigations and clinical trials that are adaptable to a wide range of ages and disorders and capture real-life social and executive deficits.

NIH Toolbox: A comprehensive set of neurobehavioral measurements that quickly assess cognitive, emotional, sensory, and motor functions from the convenience of an iPad.

> NIH Toolbox Emotion Module: A reasonably short measure of psychological well-being, general life satisfaction, meaning and purpose, self-efficacy, and social relationships. Each measure takes 1–2 minutes to complete and uses computer adaptive testing methods.

PROMIS (Patient-Reported Outcomes Measurement Information System): A set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and with individuals living with chronic conditions.

Rating Anxiety in Dementia (RAID) scale: A clinical rating scale developed to evaluate anxiety in persons with dementia.

SOBC (Science of Behavior Change) repository: A repository of behavioral science measures that have been validated (or are in the process of being validated) in accordance with the SOBC Experimental Medicine Approach. The SOBC Research Network has identified specific potential targets for behavior change interventions in the three broad domains of self-regulation, stress reactivity and stress resilience, and interpersonal and social processes.

Symptom Checklist 90-Revised (SCL-90-R®): An instrument that helps evaluate a broad range of psychological problems and symptoms of psychopathology. The SCL-90-R is also useful in measuring patient progress or treatment outcomes.

Tablet-based Cognitive Assessment Tool (TabCAT): A software platform developed at the University of California, San Francisco for the administration of clinical and research tools and for the secure storage of, and access to, the data collected. The variety of tools available on TabCAT includes cognitive tests of executive function (including NIH EXAMINER subtests), memory, visuospatial skills, and socioemotional functions, as well as symptom questionnaires. Many tests are available in multiple languages.

The Well-Being 5: A diagnostic instrument that combines elements of the Well-Being Index and Well-Being Finder. It covers six broad conceptual components: physical health, emotional health, healthy behaviors, work environment, basic access to care, and life evaluation.