NIH National Institutes of Health

NIH Music and Health

Assessing and Measuring Target Engagement:

Mechanistic and Clinical Outcome Measures for Brain Disorders of Aging

SOUND HEALTH

Friday
June 18, 2021

1:00-4:00 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.

Today's meeting, *Assessing and Measuring Target Engagement: Mechanistic and Clinical Outcome Measures for Brain Disorders of Aging,* the second in a series of three, marks the start of a new activity for the Trans-NIH Music and Health Working Group. In partnership with the Renée Fleming Foundation and the Foundation for the NIH, the working group hopes ultimately to create and share a toolkit for research on music and health across the lifespan, including a consolidated set of common data elements for music-based intervention protocols. In this series of meetings, the team is focusing first on music-based interventions for brain disorders of aging, including Alzheimer's disease and Parkinson's disease, as this area of music research provides some of the most compelling evidence for health benefit. Zeroing in on this piece of the lifespan first will focus our efforts and help create a model for future work.

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 this toolkit 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 in the months ahead. Your dedication to this work is inspiring.

Renée Fleming, Renowned Soprano, Arts and Health Advocate

Agenda

JUNE 18, 2021: 1:00–4:00 P.M. ET

1:00–1:10 p.m. **Welcome**

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

Renée Fleming, Renowned Soprano, Arts and Health Advocate

1:10–1:15 p.m. **Setting the Stage: Music-Based Interventions (MBIs) 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. **Measurement Advances: Implications for the Sound Health Initiative**

William T. Riley, Ph.D., Director, Office of Behavioral and Social Sciences Research

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*

1:50–2:10 p.m. **Question 1: What are the important considerations for selecting mechanistic and clinical outcome measures for brain disorders of aging? When designing MBIs for brain disorders of aging, what are the most important functional domains to be considered (cognition, emotion, motor, sensory, interoception)?**

2:10–2:30 p.m. **Question 2: What are the most useful mechanistic outcomes for Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD), Parkinson's disease (PD), and stroke that can be used to assess target engagement?**

- Functional imaging and functional connectivity outcomes
- Electrophysiological outcomes

- Social and behavioral outcomes
- Cognitive and physiological outcomes
- Linguistic responses/processes
- Music-centered responses/processes

2:30–2:40 p.m. **Break**

2:40–3:10 p.m. **Question 3: What are the advantages and disadvantages to be considered when prioritizing clinical outcome measures for AD/ADRD, PD, and stroke (e.g., objective, performance-based, patient-reported, functional)?**

- Prioritization based on the intervention
- Primary vs. secondary outcome measures
- Proximal vs. distal (i.e., short- and long-term) outcome measures
- Engaging participants and caregivers
- Remotely collected measures (i.e., ecological momentary assessment [EMA])
- Linguistic outcomes
- Music-centered outcomes

3:10–3:25 p.m. **Question 4: How valid and reliable are existing tools and resources (e.g., the Patient-Reported Outcomes Measurement Information System [PROMIS®], the NIH Toolbox®, Quality of Life in Neurological Disorders [Neuro-QoL™], Science of Behavior Change [SOBC]) for studying MBIs for brain disorders of aging?**

What new tools or resources are needed?

3:25–3:55 p.m. **Broad Question and Answer Session**

Videocast audience and Zoom meeting participants

3:55–4:00 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 Outcome Measures

Guiding principles and practical implementation considerations in choosing mechanistic and clinical outcome measures:

- The research question, the types and goals of the intervention, and the patient and caregiver experience (population and disease condition) are primary determinants of the choice of primary and secondary outcome measures.
- Patient-reported outcomes, mixed-methods design, and participatory methods to address contexts (race, culture, geography) should be considered.
- Attention should be given to assessing the impact of the music intervention on multiple outcomes/domains—the Thinking-Moving-Feeling triad.
- The time dimension is critical—symptom exacerbation and disease progression (i.e., in Alzheimer's disease, cognition in early stages but behavioral manifestations at middle and later stages) impact music-based intervention (MBI) outcomes, as well as the short-term, intermediary, and long-term effects of interventions.
- Measures with strong psychometric properties should be prioritized (test-retest reliability, discriminative reliability/sensitivity to change, etc.).
- Consideration should be given to the impact on subject burden and the number of outcome measures.
- 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 MBI 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 MBIs (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).

Domain	Measurable Outcomes for Alzheimer's Disease and Alzheimer's Disease Related Dementias, Parkinson's Disease, and Stroke (Not an Exhaustive List)
Emotion	Anxiety, depression, emotional regulation, affect, awe, joy, happiness, motivation, interest in life
Cognition	Language, alert states, short-term memory, long-term memory, autobiographical memory, motivation
Motor	Mobility, falls, gait speed
Sensory	Autonomic function, pain, hearing in noise
Interoception	Interoceptive awareness, accuracy
Behavioral	Aggressiveness, wandering, agitation, psychosis, apathy, impact of medication
Social	Social connection, social belonging, altruism
Engagement behaviors	Self-efficacy, music, flow, creativity, and artistic identity
Functional status	Activities of daily living, quality of life, level of independence, well-being, sleep quality
Voice/Speech	Voice quality, control, volume, level of voice output
Caregiver	Burden, emotional impact

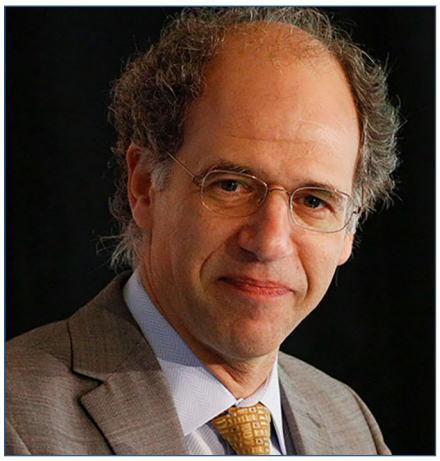
Abstract for Dr. Bill Riley's Presentation

MEASUREMENT ADVANCES: IMPLICATIONS FOR THE SOUND HEALTH INITIATIVE

This presentation addresses key considerations in choosing relevant domains and measures for assessing outcomes and intervention targets. A conceptual outcome framework is an essential step for identifying relevant domains for proximal and distal outcomes, boundary conditions (i.e., moderators), and mechanisms (i.e., mediators). For each domain, a range of measurement modalities are possible, including self-report, performance, direct observation, sensor technologies, physiological monitoring, and various functional brain measures, each of which has strengths and weaknesses for assessing the domain of interest. Therefore, multimodal assessment of a given domain is often preferable. Psychometric properties, including reliability, validity, and sensitivity to change, are important to consider in measurement selection, but these properties are dependent on the purpose and context of the assessment as well as the population under study. Modern psychometric theory (e.g., item response theory [IRT]) provides for more efficient and targeted assessments of many social and behavioral domains, and IRT approaches have been applied to the development and testing of recent National Institutes of Health (NIH)-supported measurement systems such as the Patient-Reported Outcomes Measurement Information System (PROMIS) and the NIH Toolbox. These modern psychometric approaches also provide specific linkages between different measures of the same domain, facilitating data comparison and integration across studies using different measures of the same domain. Advances in measurement are crucial to advances in science, and rigorous measurement approaches provide precise and accurate estimates of outcomes relevant to music-based interventions for brain disorders of aging.

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

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

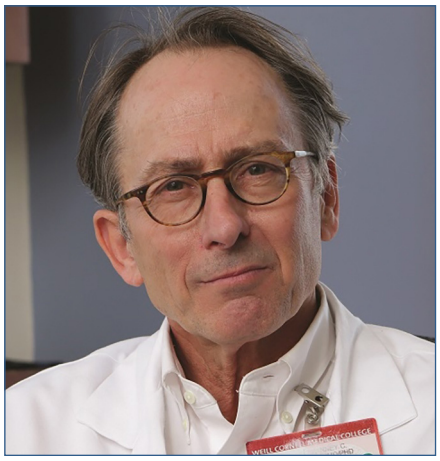
Sona Dimidjian, Ph.D., is Director of the Renée Crown Wellness Institute and professor, Department of Psychology and Neuroscience, at the University of Colorado Boulder. Dr. Dimidjian received her B.A. in psychology from the University of Chicago and a Ph.D. in clinical psychology from the University 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.

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.

Antonio Morgan-López, Ph.D., RTI International Community Health Research Division

Antonio Morgan-López, Ph.D., is a fellow in quantitative psychology in the RTI International Community Health Research Division. His work centers around the development and application of advanced quantitative methodologies, predominantly in the context of randomized and nonrandomized studies of behavioral health interventions. Dr. Morgan-López has served as principal investigator on five NIH grants since 2006, including two currently funded grants (R01AA025853, R01MH124438) that center around the joint modeling of cross-study variation in measurement and intervention effects within Integrative Data Analysis. His general methodological interests center around differential symptom functioning across populations in estimating psychiatric disorder severity under item response theory and nonlinear factor analysis, propensity score weighting for mediation and moderation analysis, and generalized nonlinear mixed modeling with random treatment effects.



Cary Reid, M.D., Ph.D., NewYork-Presbyterian/Weill Cornell Medical Center

Cary Reid, M.D., Ph.D., has practiced geriatric medicine at NewYork-Presbyterian/Weill Cornell Medical Center since 2003. He completed his residency in medicine at Dartmouth-Hitchcock Medical Center and completed fellowships in both clinical epidemiology and geriatric medicine at Yale University. He has received many research awards over the years, including a Robert Wood Johnson Foundation Generalist Physician Faculty Scholars award and a Paul Beeson Physician Faculty Scholars in Aging Research award. Dr. Reid's work in New York City at the Translational Research Institute on Pain in Later Life, which is an Edward R. Roybal Center that focuses on chronic pain and is funded by the National Institute on Aging, supports translational research on pain and aging.

Gloria Y. Yeh, M.D., M.P.H., Harvard Medical School and Beth Israel Deaconess Medical Center

Gloria Y. Yeh, M.D., M.P.H., is an associate professor of medicine at Harvard Medical School and a clinician-investigator in the Division of General Medicine at Beth Israel Deaconess Medical Center. She is the director of clinical research at the Osher Center for Integrative Medicine at Harvard Medical School and Brigham and Women's Hospital and director of the Harvard Medical School Research Fellowship in Integrative Medicine. Dr. Yeh's research expertise is on clinical trials of mind and body exercise for chronic disease, including cardiovascular and pulmonary conditions.

CLINICAL TRIALS METHODOLOGY

Eric J. Lenze, M.D., Washington University School of Medicine in St. Louis

Eric J. Lenze, M.D., is a professor of psychiatry at Washington University School of Medicine in St. Louis. He is a geriatric psychiatrist and clinical trialist with more than 20 years of experience studying pharmacologic and behavioral treatments in randomized controlled trials. He has embraced clinical trial innovations, including fully remote trials that use e-consent and incorporate mHealth techniques such as high-density measurement of patients via smartphones. Dr. Lenze has used this technique to repurpose the drug fluvoxamine for early treatment of COVID-19, and he is currently leading a

confirmatory trial that is recruiting throughout the United States and Canada. Dr. Lenze has successfully led several trials that have generated an evidence base in two areas of geriatric psychiatry. The first area is pharmacologic management of treatment-resistant depression. Dr. Lenze directs the large clinical trial "Optimizing Outcomes of Treatment-Resistant Depression in Older Adults." The second area is pharmacologic and psychological management of anxiety disorders. Other areas of Dr. Lenze's clinical trial research include testing treatments to improve age-related cognitive decline, cognitive training with vortioxetine versus placebo, and improving functional outcomes among older adults undergoing postacute rehabilitation. Dr. Lenze has published approximately 280 articles and book chapters, including more than 200 peer-reviewed papers. As a principal or coprincipal investigator, he has received approximately $51 million in funding from the Federal Government and the Patient-Centered Outcomes Research Institute. He has mentored 40 individuals, ranging from college undergraduates to junior and midcareer faculty.

Inbal Nahum-Shani, Ph.D., University of Michigan

Inbal Nahum-Shani, Ph.D., is a research associate professor at the Institute for Social Research and a founding member of the Data-Science for Dynamic Decision-Making Lab (D3 Lab) at the University of Michigan. Her research focuses on conceptual and methodological issues pertaining to the construction of effective adaptive interventions, a treatment design in which ongoing information from the person is used to individualize the type, dose, and modality of support or treatment, and to just-in-time adaptive interventions, a special form of adaptive intervention in which mobile devices are used to provide support in a timely and ecological manner. Dr. Nahum-Shani collaborates with multiple scientific teams on the development of technology-based interventions that deliver support in real time, including interventions for engaging individuals in self-monitoring behaviors, emotion-regulation exercises, and mental health treatments. Dr. Nahum-Shani provides leadership for three federally funded research projects to inform the development of adaptive interventions and just-in-time adaptive interventions targeting substance use (funded by the National Institute on Drug Abuse), obesity (funded by the National Institute of Diabetes and Digestive and Kidney Diseases), and smoking (funded by the National Cancer Institute).

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.

Jeff D. Williamson, M.D., Wake Forest School of Medicine

Jeff D. Williamson, M.D., is professor of internal medicine and epidemiology, and chief, Section on Gerontology and Geriatric Medicine, at Wake Forest School of Medicine. He is an internationally known geriatrician and clinical trialist. He also serves as director of the Center for Healthcare Innovation. He is coleader of the Alzheimer's Disease Research Center and clinical core leader for the Wake Forest Claude Pepper Older Americans Independence Center. Dr. Williamson received his medical degree from the Medical College of Georgia and a master's degree in epidemiology from the Johns Hopkins University School of Hygiene and Public Health. He completed a fellowship in geriatric medicine at Johns Hopkins. Dr. Williamson's primary research interests are in understanding relationships between chronic diseases such as hypertension and diabetes and maintaining brain health and physical function in aging adults, the prevention of aging-related loss of independence, and developing research methods for including elderly persons in clinical trials.

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*.

Gammon M. Earhart, P.T., Ph.D., FAPTA, Washington University in St. Louis School of Medicine

Gammon M. Earhart, P.T., Ph.D., FAPTA, is associate dean for physical therapy, director of the Program in Physical Therapy, and professor of physical therapy, neuroscience, and neurology at Washington University in St. Louis School of Medicine. She is a physical therapist and movement scientist. Dr. Earhart's research focuses on motor control and neurorehabilitation in neurodegenerative conditions, with an emphasis on use of music and dance to enhance movement among people with Parkinson's disease.

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.

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.

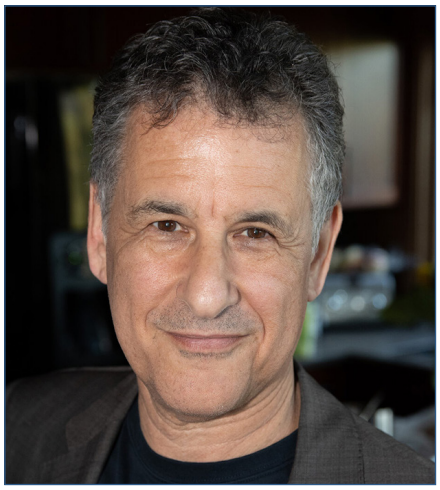
NEUROSCIENCE

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.

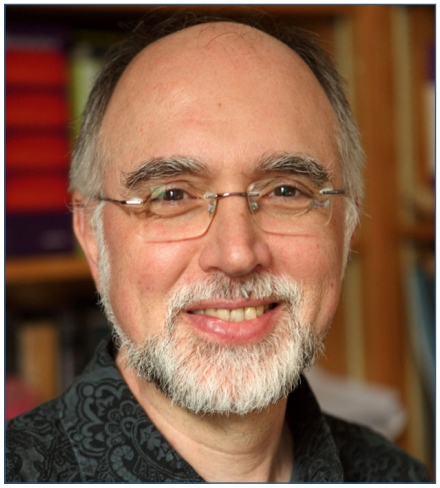


Daniel J. Levitin, Ph.D., McGill University

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.

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.



Robert J. Zatorre, Ph.D., McGill University

Robert J. Zatorre, Ph.D., is a cognitive neuroscientist at the Montreal Neurological Institute of McGill University. He was born and raised in Buenos Aires, Argentina, and carried out his doctoral studies at Brown University with the late Peter Eimas, followed by postdoctoral work with Brenda Milner. He currently holds a Canada research chair at the Montreal Neurological Institute of McGill University. In 2006 he became the founding codirector, with Isabelle Peretz, of the international laboratory for Brain, Music, and Sound Research. His work has been recognized with several awards, including the Ipsen Foundation prize in neuronal plasticity in 2011, the Knowles prize in hearing research from Northwestern University in 2013, election to the Royal Society of Canada in 2017, and the de Carvalho-Heineken prize in cognitive science from the Netherlands Academy of Arts and Sciences in 2020. He is also a fellow of the Canadian Institute for Advanced Research. Dr. Zatorre's lab studies the neural substrates of auditory cognition, with special emphasis on two complex and characteristically human abilities: speech and music. With his collaborators and students, Dr. Zatorre has published more than 300 scientific papers on topics including pitch and melody perception, auditory imagery, music production, brain plasticity in musicians, and the role of the dopaminergic reward circuitry in mediating musical pleasure. His research spans all aspects of human auditory processing, from the functional and anatomical properties of auditory cortex and its connectivity to how these properties differ between the hemispheres and how they change with training or sensory loss. Examples of recent research projects include using graph theory models to understand anatomical connectivity of the auditory cortex from magnetic resonance diffusion data, using magnetoencephalography to track the cortical and subcortical responses to periodicity, applying machine learning algorithms to functional magnetic resonance imaging (fMRI) to investigate reward-related brain activity to music, demonstrating hemispheric asymmetries in fMRI activity to speech and melody in relation to spectrotemporal modulations, and application of brain stimulation paradigms to enhance auditory working memory and to modify hedonic responses to music. Dr. Zatorre's

activities are funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, the Canada First Research Excellence Fund, and the Canadian Institute for Advanced Research.

PATIENT ADVOCACY AND ARTS ORGANIZATIONS

Melani Dizon, M.A., M.Ed., Phinney Foundation for Parkinson's

Melani Dizon, M.A., M.Ed., is director of education and research, Davis Phinney Foundation for Parkinson's. She joined the foundation in January 2018. She's a former social worker, teacher, and therapist and has worked as a freelance educator and writer for over 25 years. Ms. Dizon is a Parkinson's advocate and deeply committed to patient education. She heads up the educational and research initiatives for the foundation and works very closely with people living with Parkinson's disease and their care partners to help them design their ideal plan for living well today.

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.

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.

Heather M. Snyder, Ph.D., Alzheimer's Association

Heather M. Snyder, Ph.D., is the vice president of medical and scientific relations at the Alzheimer's Association. In this role, she oversees association initiatives that accelerate innovative Alzheimer's research and provide opportunities for the global dementia community to connect and collaborate. Dr. Snyder is responsible for the progress the association has made in Alzheimer's disease and dementia research funding. She leads the association's International Research Grant Program, the vehicle through which the association funds promising investigations that advance understanding of Alzheimer's disease and moves the field toward solutions for the global Alzheimer's disease crisis. As the world's largest nonprofit funder of Alzheimer's disease research, the association is currently investing $167 million in more than 500 active, best-of-field projects in 27 countries. As part of this effort, Dr. Snyder is instrumental in advancing grant programs that explore sex- and gender-based disease vulnerability. These grant programs contributed to the Women's Alzheimer's Research Initiative, one of the only focused funding programs in this area. The programs also fund studies to uncover how biological and genetic factors shape disease development and progression in women as compared to men, a factor that may influence diagnostic and treatment options as research moves closer to precision medicine. To increase knowledge about prevention and risk reduction, Dr. Snyder serves on the executive team for the U.S. Study to Protect Brain Health Through Lifestyle Intervention To Reduce Risk. In addition, she oversees the development and management of the Alzheimer's Association's leading clinical

neurology journal, *Alzheimer's and Dementia,* and its companion open-access journals, which help bridge the knowledge gaps across a wide range of dementia research disciplines. Dr. Snyder sits on the programmatic review committee for the U.S. Department of Defense Congressionally Directed Medical Research Programs for Alzheimer's disease. She has been a peer reviewer for NIH, the Polish government, the Centers for Disease Control and Prevention, and California's Alzheimer's disease funding program. An expert in the field, Dr. Snyder has been featured in numerous television interviews, including the Dr. Oz Show, and in news articles in *The New York Times*, *The Washington Post*, *Crain's Chicago Business* "40 Under 40," and the *Wall Street Journal*. She holds a Ph.D. in molecular biology from Loyola University Chicago Stritch School of Medicine and a bachelor's degree in biology and religious studies from the University of Virginia.

Group Abstracts

BEHAVIORAL AND SOCIAL SCIENCE INTERVENTION DEVELOPMENT

Group members:

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

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

Antonio Morgan-López, Ph.D., RTI International

Cary Reid, M.D., Ph.D., NewYork-Presbyterian Hospital/Weill Cornell Medical Center

Gloria Yeh, M.D., M.P.H., Harvard Medical School and Beth Israel Deaconess Medical Center

Music is often made and listened to with others. Given that from an evolutionary perspective social cohesion and cooperation are considered one of the primary functions of music and that social isolation is often reported among older adults, inclusion of measures focused on social interaction, social belonging, community engagement, interpersonal relationships, and overall quality of life is considered high priority for music-based interventions (MBIs) targeting older adults. Additionally, and specifically in relation to Alzheimer's or Parkinson's disease, outcome measures that capture symptoms in the disease domains of interest and contribute to potential medication-sparing effects are also considered important. Of note, music-based interventions are broad and heterogeneous, ranging from passive music listening to active group chorale singing or drumming circles, or creation of individualized lyrics, and thus it is relevant for the designed outcome measures to parallel the active ingredients of specific MBIs.

In terms of measures to assess engagement of the intended study populations, qualitative measures and self-report are thought to be relevant and can contribute significantly to understanding whether and how programs work. Measures of self-efficacy and social motivation and belonging may be effectively used to assess target engagement. Target population needs and limitations should be considered with care. For example, given that the populations being discussed are relatively vulnerable, one important factor to consider in designing measurements is the high risk of subject burden. Potential symptom exacerbation is another consideration. For example, asking older adults without prior music training to engage in music making in a public context can result in transient social anxiety in the participants and avoidance of future participation if not well accounted for in the design of the implementation. Another important factor to consider is the potential for contributing to harm, particularly when targeting populations who have limited motor capacities and high fall risk, such as Alzheimer's and Parkinson's disease populations. Other potential measures to consider are methods based in genetics and epigenetics, given variability among people in their musical preferences. In addition, measures of body awareness and interoception may be very relevant to examine with MBIs and give insight into neuromechanistic pathways. In

general, identifying common measures across studies that allow for documenting change over time and that can assess intermediary and long-term improvement or deterioration at the individual level is needed.

In designing new measures, it is practical to take advantage of existing initiatives such as the Patient-Reported Outcomes Measurement Information System (PROMIS) and the Computerized Adaptive Testing for Mental Health Disorders (CAT-MH™) modules to place the right pieces into a new relevant toolbox for MBIs. For example, PROMIS has many different surveys and questionnaires that are in the domains of interest for MBI studies, including physical function, sleep, and fatigue. In addition, using psychometric measures of how individual symptoms relate to disorders is important to consider, and to the extent possible, using existing computer adaptive testing and modules for burden reduction is advised. Also, participatory methods to guide measurement decisions are of value in ensuring that studies address contexts such as race, culture, and geography in understanding how participants identify and respond differently to MBIs. Secondary measures that can be considered include program participation and intent to continue engagement with music. Other initiatives, such as the Science of Behavior Change (SOBC), also provide a relevant existing framework to consider target outcomes and mechanistic pathways when studying MBIs. Ultimately, the research question, the specific MBI, the population, and what a particular study is trying to examine are the most important factors in determining the relevant outcome measures.

Music is multifaceted and complex, and music-based interventions are wide ranging. The considerations detailed above will assist in maximizing our efforts to better understand the mechanisms of change associated with music interventions.

CLINICAL TRIALS METHODOLOGY

Group members:

Eric J. Lenze, M.D., Washington University School of Medicine in St. Louis

Inbal Nahum-Shani, Ph.D., University of Michigan

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

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

Jeff D. Williamson, M.D., Wake Forest School of Medicine

When designing music-based interventions (MBIs) for brain disorders of aging, important functional domains to be considered include motor, cognitive, emotion (including affect and sense of control), and social function (including social support, social isolation, and loneliness). The focus on a particular domain could change depending on the stage/progression of the disease. For example, in the beginning phases of Alzheimer's disease, the focus could be on cognition, but as the disease progresses, emotional and behavioral domains may become more salient. It would be important not to narrow the focus to a single domain. Adaptive interventions may be used as a framework for organizing

efforts to focus on multiple domains in a single MBI package. An adaptive intervention is a sequence of treatments that are tailored to address the specific and changing needs of individuals; MBI components can be sequenced and tailored to focus on the domain(s) most important for the individual at a given point in time.

Useful outcome measures that can be used to assess target engagement may include short-term and possibly long-term function, including "nonmotor" symptoms (e.g., autonomic function and pain), motor function (e.g., gait, balance, speech), cognitive functions (e.g., attention, memory), mood (e.g., depression, anxiety), activities of daily living (e.g., dressing, bathing), and behavioral outcomes (e.g., agitation, aggressiveness, apathy, paranoia). Milestones such as loss of independence, the need for institutionalization, or the number of falls, fractures, or emergency department visits may serve as outcomes that have significant personal consequences but are not included in standardized rating scales (although they have become increasingly accessible through electronic health records). Other outcome measures to consider include social interactions, sleep quality, voice quality, quality of life, a treatment's duration of benefit (often used in studies of medications for Parkinson's disease), and engagement with the intervention. It is important to consider outcomes for both patients and caregivers, and their interactions. This can provide opportunities to address caregiver needs. Outcomes specific to caregivers may include caregiver stress and burnout.

Regarding prioritizing clinical outcome measures, given that MBIs can influence people in many domains, it might be useful to focus on how the intervention can be designed to target multiple domains and outcomes. This would involve identifying the primary distal outcome (i.e., the ultimate goal the intervention is intended to achieve given the specific population and problem to be addressed), specifying a scientific model that includes various mechanisms of change that can be helped via music-based therapy, and identifying specific intervention components that can address each mechanism. Prioritizing outcomes and mechanisms to be measured would ideally be based on the key scientific questions motivating the study. It is critical to develop measures that are reliable, sensitive to change, and practical given the target population. For example, standardized scoring measures may not be applicable to people with cognitive impairment; rather than asking participants to answer a standardized set of questions, investigators could use spoken responses from participants about what bothers them. Reports from both patients and caregivers may be needed to measure certain outcomes.

Regarding existing and new tools/resources, advances in mobile and wearable devices offer many opportunities to measure mechanisms and outcomes continuously and unobtrusively. Existing mobile and wearable devices used in studies with older adults could be repurposed to measure outcomes of MBIs; research to develop new technology-based measures is needed.

MUSIC THERAPY/MUSIC MEDICINE

Group members:

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

Gammon Earhart, P.T., Ph.D., Washington University in St. Louis School of Medicine

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

Michael Thaut, Ph.D., University of Toronto

Our subgroup was asked to respond to four topics during the premeeting breakout group on May 10, 2021. For the purposes of our discussion, brain disorders of aging included Parkinson's disease (PD), Alzheimer's disease and related dementias (AD/ADRD), and stroke.

Discussion about the most important functional domains and most useful outcome measures occurred during all topic prompts. The table below summarizes our recommendations. (Note: this is not a comprehensive list.) We raised additional considerations related to whether we should focus on managing symptoms versus disease-modifying effects of music-based interventions (MBIs). We also pointed out that there are interactions among domains and that brain diseases of aging affect multiple domains. In addition, key domains change as brain disorders of aging progress.

During the discussion of outcome measures, we discussed the importance of including clinically meaningful outcome measures, although combining mechanistic or neurologic measures with clinically meaningful outcomes also would be useful. Selecting outcomes that document behaviors that change with disease progression was also suggested. Developmental work related to outcome measures is needed, and it is important not to assume that current outcome measures will be the most useful or appropriate. Using qualitative methods may help. Measuring constructs of joy, happiness, vitality, and nostalgia and moment-to-moment experiences may also be important outcomes, but there is an absence of validated measures. We also noted the absence of good measures to assess music-related outcomes (e.g., flow, creativity, and artistic identity).

Primary outcomes should be chosen based on the intervention content and theoretical framework, with acknowledgment that many MBIs target multiple domains. Although music is multimodal, primary outcomes can be identified. We also emphasized the importance of considering outcomes for caregivers, as engagement of the caregiver can impact adherence, both people may benefit (e.g., better relationship), and caregivers could help the patient continue the therapy at home. The needs to distinguish proximal outcomes from distal ones and consider the intensity and duration of the MBIs and outcomes were also emphasized.

Domain	Outcome Measure Examples	Relevant Condition(s)
Emotion	Anxiety, depression	All
Behavioral	Wandering, agitation, psychosis, apathy, behavioral state outcomes, engagement behaviors (interactions with other people or the environment)	AD
Cognition	Language, neuropsychological, alert states	All
Motor/sensory	Mobility, falls	PD, stroke, non-AD
Interoception		PD
Well-being	Quality of life	All
Activities of daily living		TBD
Symptoms	Sleep, pain	All
Voice	Voice quality, control	PD
Caregiver	Burden	All
	Neurologic measures	TBD

NEUROSCIENCE

Group members:

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

Nina Kraus, Ph.D., Northwestern University

Daniel Levitin, Ph.D., McGill University

Josh McDermott, Ph.D., University of Minnesota

Robert Zatorre, Ph.D., McGill University

The essence of music is sound. The brain system involved in sound is hearing. The hearing brain has especially deep interconnections with brain centers involved in the domains of emotion, cognition, motor, interoception, and other senses. Thus, all these domains need to be considered. Music is very much an interpersonal intervention. Music connects people with each other and with the world. It may improve interaction with caregivers and family members, and in diseases of aging, caregivers and family members are almost as important as the patient. Consequently, music-based interventions (MBIs), with sound at their core, are a compelling route to pursue in the rehabilitation of disorders of aging.

It is challenging to enforce standards in the delivery of an MBI. If you simplify the intervention for a study, you lose some of the essence of music, but if you stick with the version used by music therapists in everyday practice, it can be difficult to codify. The interactivity among patient, practitioner, and the music itself is impossible to fully control for. Likewise, music defies controlled dosing as is possible in a drug trial. Finally, with the system-spanning sensory, motor, and cognitive involvement of music, appropriate control conditions make traditional randomized controlled trials challenging.

Practitioners of MBIs, such as music therapists, typically are not basic scientists and have not been trained in the design of rigorous scientific studies. Indeed, it has been noted that many past MBI applications to NIH lacked rigor. Therefore, it is important to offer guidance to ensure that research into MBIs meets the rigorous standards necessary to warrant interest from NIH.

A few things have been identified as essential guidance to convey to prospective applicants:

1. ***Research questions should be mechanistic.*** It is not sufficient to hypothesize that "MBI X helps improve condition Z." In the absence of a mechanistic hypothesis, such as "MBI X affects physiological process Y, which leads to improvements in condition Z," we cannot know the "why," and a negative result teaches us little.

2. ***A physiological outcome is not enough.*** Improving patient outcomes is paramount.

3. ***Rigor can be maintained in the outcomes.*** While research questions and approaches in music research might defy standardization, outcomes can and should be standardized. Ongoing meetings of the neuroscience group will examine existing tools such as the NIH Toolbox and NINDS's common data elements (CDEs) and recommend and develop improved outcome measures. If four studies use four different MBIs in an attempt to improve a particular outcome Z in patients with Alzheimer's disease and each uses a different instrument to measure Z, the knowledge gained is ambiguous. However, if each uses *Assessment Tool A* because we offer guidance that A is the gold standard in the assessment of Z, there is a basis to compare interventions. Categories we should codify and offer guidance on include, but are not limited to:

    a. Short-term memory

    b. Listening in noise

    c. Emotional health

    d. Motor ability

    e. Physiologic measures of brain health

Guidelines should promote creativity while helping investigators focus on rigorous, well-targeted research questions with defined and standardized outcomes. We must use caution not to provide guidance that limits research, such as restrictively defining what qualifies as music. In time, with sustained NIH investment in music research, 1) the field will learn from the experiences with the early grants and 2) well-qualified researchers will enter this space, performing rigorous studies. This will create a self-sustaining positive cycle where music therapists and other clinicians can do postdoctoral fellowships in established laboratories where they learn about research methods and produce rigorous proposals in the future.

PATIENT AND ARTS ADVOCACY

Group members:

Melani Dizon, M.A., M.Ed., Davis Phinney Foundation for Parkinson's

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

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

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

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

Heather Snyder, Ph.D., Alzheimer's Association

Question 1: When designing music-based interventions (MBIs)…, what are the most important functional domains to be considered?

Interdependencies among functional domains in the context of MBIs exist. Patient and/or caregiver needs, intervention impact, and response may vary, and separation of a primary domain from other domains may not make sense. From the caregiver's perspective, behavior may be a primary interest. Where cognition is the target domain of interest, a challenge researchers face is demonstrating cognitive change and the relative contribution of the MBI to identified cognitive changes or retention of cognitive abilities.

Primary and Cascading Domain Responses With Music Therapy (MT). Multiple areas should be considered, such as mood, emotion, sense of well-being, and sensory-motor integration. In the example of Parkinson's disease (PD), the motor domain is a primary interest, e.g., cuing, rhythm, and Rhythmic Auditory Stimulation. The patient's lived experience should be considered with respect to study outcomes and from multiple domain perspectives. General well-being and quality of life (QoL) should be incorporated into studies from the patient and caregiver points of view. In targeting gait in PD, a patient might feel a sense of accomplishment or happiness during the MBI, which then might affect nonmotor symptoms, such as depression. The MBI and interaction with the therapist and/or group may result in significant observed joy and social connection affecting QoL, motivation, and readiness for treatment. A cascading effect from the primary domain (i.e., physical motor) affecting emotional regulation may serve as a biological measure of MBI efficacy. Related physiological changes in response to sensory stimuli could be measured via laboratory studies.

Endophenotypes. A contrasting perspective that may be useful as part of a toolkit is to not only consider a set of symptoms tied to a disease state but to target endophenotypes that many diseases have in common.

Traditional Functional Scales. Use of traditional functional scales can be problematic, e.g., the Clinical Dementia Rating (CDR) in Alzheimer's disease (AD) may not detect/capture changes in emotional state when the patient is exposed to MBIs. Further, even a highly successful intervention that changes mood and QoL for the patient and caregiver might not show change on the CDR. Functional measures specific to the intervention and study group may be needed. Therefore, validated music-based scales are useful, although few

exist. Differences in detection/sensitivity are sometimes observed in practice when assessed using a music-based instrument versus a traditional functional measure. This occurs in the clinic between disciplines where MBIs elicit greater response in some domains (e.g., ability to sequence/cognitive domain). (For an example tool see Music in Dementia Assessment Scales [MiDAS].)

Domains and Suitability of Mixed Methods. Given the desire for discrete, functional, and measurable domains and concepts, the patient, caregiver, or therapist experience is not always neatly categorized by the metrics. Self-reporting features of the phenomena under study may be necessary. Therefore, mixed-methods designs may be important for some questions, with analyses by disease stage and acuity within domains.

Biomarkers. Neurofilament light chain (NFL) is released from the axon with the onset of the neurodegenerative process, and plasma NFL rises early in the course of frontotemporal dementia. NFL is also a promising biomarker for neurodegeneration in AD, but it is a less robust biomarker for PD. With AD there are also biomarkers for amyloid and tau that can be measured in the blood, if disease modification is expected. Other biomarkers related to the synapse (e.g., synaptophysin) may merit consideration as part of trials, although further work with these measures is still needed. Neuroimaging is actively used in clinical trials, and progressive brain atrophy is measurable over the course of a year with AD. Functional connectivity mapping could be used to detect the functional brain networks that improve with an intervention, although by itself it would not be proof of the efficacy of an intervention. Even if a profound functional change is not seen, such as with a CDR, it may be important to show evidence of biomarkers intervening in the disease process, perhaps even more so than with functional magnetic resonance imaging change, given its interpretation difficulties.

Mechanistic Hypotheses. Mechanistic hypotheses (e.g., a circuit or set of molecules underpinning a functional domain) were considered important. In short, outlining the conceptual framework and the cyclic process, from the applied clinician's perspective, to the advocate and caregiver perspectives, to the underlying biomarkers and what is happening mechanistically offers a comprehensive line of research on the topic/question.

Caregiver-Patient Dyad. Caregivers' QoL is an important measure in clinical trials. Caregiver perspectives inform behavior change in patients. Moreover, when caregiver mental health is affected, patient lifespan is affected. Culturally appropriate and tailored MBIs targeting the dyad team may influence multiple domains.

Question 2: What are the most useful outcome measures that can be used to assess target engagement?

Music-Based Outcome Measures and Technologies. Valid and comparable music-based outcome measures are needed. Existing motor scales in PD could be paired with music therapy protocols; however, as noted, better functional scales for trials of MBIs are needed. Emerging technologies supporting outcome measurement may be useful and efficient, e.g., large online music groups captured on recordings can be analyzed for readouts of emotion, assessing measurements of perception, emotional regulation, and changes in awe and altruism (Levenson lab). Similarly, technologies for the analysis of voice quality and detection

of changes in response to MBIs are especially important for PD patients. Voice recordings are used in current studies (R. Au, E. Haneishi) to assess cognition and functioning and possibly predict risk of AD.

Advances in artificial intelligence might be considered in clinical trials to measure facial movements and emotions. This may be a useful strategy area, such as changes in facial masking in PD under MT. Some current trials of interventions other than MT use continuous at-home monitoring, such as actigraphy, for accurate measurements. Other physiological biomarkers, like heart-rate variability and parasympathetic tone, might supply evidence of a successful intervention around social well-being. Application to MT studies may accelerate and improve outcome detection and measurement, and data from functional imaging and functional connectivity measures may correlate with MBI effectiveness.

Disease Stage and Outcome Selection. Disease stage should be considered when identifying outcome measures, e.g., outcomes in advanced AD may focus on QoL, stress, and behavioral disturbances. Outcome measures for earlier stages of the disease may focus on improving/maintaining cognition and function and/or slowing decline.

Question 3: What are the advantages and disadvantages for consideration when prioritizing clinical outcome measures?

Remote vs. In-Person. Remotely collected measures help participant recruitment and data attainment when mobility is limited. Some measures can be assessed well remotely, e.g., caregiver well-being, caregiver burden, and patient scales. Cognitive and movement measures have been difficult and unreliable to assess remotely. Similarly, neurocognitive assessments have been difficult to conduct over the phone during the pandemic, and participants still need to attend in-person assessments. In contrast, there are advantages to home visits for assessment/measurement. Some interventions taking place in a group setting, e.g., PD movement and music groups, can sometimes support assessment as part of the group using available technology, e.g., group cycling classes and wearables.

Other Factors. Organization and oversight of large-scale trials is a factor for consideration bordering health services research but with relevance given to varied models of MT practice and delivery. Additionally, durability of response can be short-lived in PD patients, and the extent to which medication influences outcomes is a consideration. Even if a durable result is not achieved for an MBI, there may still be crossover to secondary outcomes, e.g., emotional, QoL, and caregiver outcomes. Improvement may not be detected, but habilitative outcomes, e.g., maintenance of function or rate of decline/change, are important perspectives for consideration.

Scalability. Studies must consider scalability since a one-size-fits-all approach is unlikely. A tailored approach within a framework protocol is feasible and is used in MT trials (e.g., Baker et al.; Robb et al.).

Question 4. How useful are existing tools/resources for studying MBIs? What new tools/resources are needed?

Existing Tools. NIH-EXAMINER was identified as a good tool for executive function that correlates with functional behavior in the home/community. The use of selected techniques in neurologic MT targeting executive function may be a promising area of inquiry.

Tools for Unmet Needs. A tool that measures moment-to-moment mood and the physiology of well-being *in situ* would be useful given variation in typical MT practice settings. Metrics on heart rate variability to indicate vagal tone in parasympathetic vs. fear or flight states may be useful, especially in some patients/phenotypes. Physiologic measures and biomarkers associated with health-related QoL may be useful in MT studies.

Panelists' Questions

1. Music-Based Interventions (MBIs) have the potential to manage symptoms, slow disease progression, rehabilitate, and improve quality of life. When designing MBIs for brain disorders of aging, what are the most important functional domains to be considered (e.g., emotion, cognition, motor, sensory, interoception)?
2. What are the most useful outcome measures (physiological, behavioral, etc.) that can be used to assess target engagement?
    - Functional imaging and functional connectivity measures
    - Electrophysiological measures
    - Social and behavioral measures
    - Psychological and physiological measures
    - Linguistic measures
    - Music-centered outcome measures
3. What are the advantages and disadvantages to be considered when prioritizing clinical outcome measures (e.g., objective, performance-based, patient-reported, functional)?
    - Prioritization based on the intervention
    - Proximal vs. distal (i.e., short- and long-term) outcome measures
    - Primary vs. secondary outcome measures
    - Engaging participants and caregivers
    - Remotely collected measures (i.e., ecological momentary assessment [EMA])
4. How useful are existing tools and resources (e.g., the Patient-Reported Outcomes Measurement Information System [PROMIS], the NIH Toolbox, Quality of Life in Neurological Disorders [NeuroQoL], Science of Behavior Chance [SOBC]) for studying MBIs for brain disorders of aging? What new tools or resources are needed?

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Suggested Resources

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.

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.

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 is adaptable to a wide range of ages and disorders and captures 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.

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.

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.

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.

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.