Mitigating Health Disparities in Brain Disorders Starting with Basic Science

Proceedings of a Workshop—in Brief

Despite increased attention paid to health equity in recent years, disparities in health outcomes and access to care persist across disease areas, including in central nervous system (CNS) disorders. Mitigating these disparities will likely require intentional efforts across the neuroscience research community to promote equitable practices and include individuals with lived/living experience and historically underrepresented communities as participants and researchers. "All of science profits by having diverse perspectives," said Walter Koroshetz, the director of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH). Convening experts who are diverse in thought, identity, and lived/living experience may galvanize discussions of strategies to reduce and prevent disparities by moving toward more equitable practices.

John Krystal, the Robert L. McNeil, Jr. Professor of Translational Research, chair of the Department of Psychiatry at Yale University, and chief of psychiatry and behavioral health at Yale New Haven Hospital, explained that the National Academies of Sciences, Engineering, and Medicine's (the National Academies') Forum on Neuroscience and Nervous System Disorders (Neuroscience Forum) hosted a workshop series in 2021 on neuroscience training that addressed such topics as racial justice (systemic treatment that results in equitable, fair, and accessible opportunities for all [National Education Association, 2021]), diversity, equity, and inclusion.[1] That activity led to a workshop series in the spring of 2023 titled Addressing Health Disparities in Central Nervous System Disorders,[2] which reviewed the current knowledge regarding health disparities in CNS disorders, explored the impact of psychosocial and environmental factors, considered models of inclusive research approaches, and discussed potential cross-disciplinary collaborations that may be needed to further elucidate these topics.

While interventions to eliminate health disparities[3] and move towards neurologic health equity[4] may benefit

[1] To learn more about the Neuroscience Training series, see https://www.nationalacademies.org/our-work/neuroscience-training-developing-a-nimble-and-versatile-workforce-a-virtual-workshop-series (accessed December 4, 2023).
[2] To learn more about the Addressing Health Disparities in Central Nervous Systems Disorders virtual workshop series, please visit https://nap.nationalacademies.org/resource/27186/interactive/ (accessed December 4, 2023).
[3] The term health disparities in this manuscript are defined as a "particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage" as provided by Healthy People 2023. For more information, see https://health.gov/healthypeople/priority-areas/health-equity-healthy-people-2030 (accessed January 10, 2024).
[4] The term health equity in this manuscript is defined as "the attainment of the highest level of health for all people… requiring valuing everyone equally with focused and ongoing societal efforts to…eliminate health and health care disparities" as provided by Health People 2023. For more

from a multilayered, interdisciplinary approach that addresses each interdependent factor (Rosendale, 2022), a sometimes-overlooked issue is the need to act within basic science by diversifying both models for research and the scientific workforce, said Sheena Posey Norris, the director of the Neuroscience Forum and a senior program officer at the National Academies, in reflecting on perspectives shared by participants at the previous workshops related to health disparities. "The persistent oversight among researchers to recognize how the lack of diverse representation in study cohorts has biased and compromised findings," Posey Norris continued, and encouraging basic scientists to engage global partners, including both researchers and individuals with lived/living experience, may improve the field's understanding of CNS disorders and treatments. Developing questions and procedures through community engagement strategies, such as community-based participatory research (CBPR), may assist in developing genuine and lasting partnerships with individuals with lived/living experience, which in turn may help tailor studies to focus on the most salient issues from the patient's perspective (Brown et al., 2019).

The Neuroscience Forum's workshop series in 2021 and 2023 set the stage for the present workshop, which focused on opportunities for the basic science research community to mitigate health disparities in neurological disorders. Posey Norris presented the overarching goal of the workshop, which was to explore how the basic neuroscience research community could improve neurobiological understanding of CNS disorders and treatments by using a health equity lens. Discussions would focus on the methodologies that neuroscientists could use to improve data quality by engaging more diverse populations in the research process; acknowledge systematic, technological, and internal biases; and consider inclusive, interdisciplinary research models to reduce the occurrence of health disparities (Box 1). This workshop highlighted a few examples of populations affected by health disparities in hopes of illuminating the barriers faced by numerous groups who do not receive equitable representation in neuroscience and CNS research.

information, see https://health.gov/healthypeople/priority-areas/health-equity-healthy-people-2030 (accessed January 10, 2024).

TERMINOLOGY AND PROXY MEASURES IN NEUROSCIENCE RESEARCH

Several workshop speakers said that opportunities to apply equitable practices in the basic science research community extend beyond the bench scientists working in laboratories. Shari Wiseman, the chief editor of *Nature Neuroscience*, spoke about the importance of transparency and reporting in research, which includes using the correct terminology to reflect biological and social differences. She emphasized that this distinction is especially necessary when reporting on race (a social construct which may provide insight on lived/living experience) and ancestry (which is more closely related to genetics) because conflating the two terms, which are often used synonymously, may perpetuate biases.

Ekemini Riley, the founder and president of the Coalition for Aligning Science and the managing director of Aligning Science Across Parkinson's, complemented Wiseman's comments by explaining that race is currently used as a proxy for disease prevalence, diagnosis, and outcomes despite the absence of evidence that race can explain biologic differences. Therefore, the focus of current and future research should be identifying biological, genetic, and molecular mechanisms of the disease. Moving forward, she said that the goal is to develop clinical trials that can eventually achieve targeted therapies that are based on the expression of specific proteins rather than race. Until science reaches a point where race and ethnicity are no longer needed, Riley said, understanding and using the correct terminology specifically and accurately will be essential to describing people in scientific literature and prevent misinterpretation of biological data.

"There has been a major push toward health equity research as opposed to health disparities research," said Kacie Deters, an assistant professor in the Department of Integrative Biology and Physiology at the University of California, Los Angeles. Race and ethnicity are often added as factors to research studies that were not designed with equity in mind, Deters said, and the outcomes resulting from this approach can be damaging to racialized communities.[5] She continued by explaining

[5] Racialized person(s) or communities are those who are affected by the process of racism or discrimination. For more information, see

BOX 1
HIGHLIGHTS

- Using accurate terminology, especially when referring to social constructs (i.e., race and gender) compared with biological differences (i.e., ancestry and sex) produces more accurate reporting of differences between groups. (Wiseman)
- There is interest in eventually moving away from proxy measures (e.g., race) and instead using targeted, objective measures of specific biological mechanisms in neurological research. (Riley)
- Examining biologic material from African Americans has allowed scientists to have a more holistic understanding of central nervous systems (CNS) disorders such as Alzheimer's disease. That understanding has the potential to increase with examination of biologic material from more communities that are underrepresented in neurological research. (Weinberger)
- Health equity research can be difficult and complex. Therefore, researchers may benefit from collaborating with health equity experts as opposed to simply adding more social factors to previously established methods. (Deters)
- There is a growing need for additional animal models that not only facilitate the study of mechanisms underlying health disparities in CNS disorders but also contribute to achieving health equity by producing more diverse basic research. (Posey Norris)
- Scientific research and clinical trials may benefit from actively engaging people with lived/living experience as collaborators in the design and communication of studies. (Gutis)
- Developing a scientific workforce that is reflective of the populations that they serve is a key to building trust with communities that may be underrepresented in science. (Koroshetz)

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

that research in racialized and minoritized populations must be intentional about examining social and genetic risks and their potential intersection(s) to prevent any misunderstanding that there is a biological basis for race (which is purely a social construct). Deters suggested that researchers collaborate with experts who specialize in health equity research to help prevent the conflation of social and biological differences.

DIVERSE REPRESENTATION IN BIOLOGICAL MATERIALS AND CLINICAL TRIALS

Biomedical research has largely centered on White males, said both Wiseman and Deters. Daniel Weinberger, the director and chief executive officer of the Lieber Institute for Brain Development and a professor of psychiatry, neurology, neuroscience, and genetic medicine at the Johns Hopkins University School of Medicine, spoke about the rejection of studies including African Americans that he had proposed earlier in his career. He attributed this rejection to the belief that the genomes of individuals with African ancestry would be "more complicated" than those of individuals with European ancestry, which would increase the difficulty of finding the genes for common illnesses. Now, the Lieber Institute for Brain Development[6] has received 4,000 donations of human brains, with 700 of them

https://www.ohrc.on.ca/en/racial-discrimination-race-and-racism-fact-sheet (accessed January 10, 2024).

[6] To learn more about the Lieber Institute for Brain Development, see https://www.libd.org/ (accessed December 4, 2023).

coming from African American individuals, Weinberger said. This has led to the development of the African Ancestry Neuroscience Research Initiative,[7] which was developed in collaboration with Morgan State University, a historically Black university, and an African American faith-based community in Baltimore, Maryland, he added.

The use of more diverse biologic material in basic neuroscience research is not only important to achieve health equity but also improves the quality of the science, Wiseman said. Weinberger said that "many brain disorders vary in their frequency and severity based on an individual's ancestry, which is their genetic lineage." An individual's genetic variation can determine how susceptible they may be to a disease or environmental factors. For example, he said, the average African American has between 0 and 60 percent European ancestry, and "Your proportion of ancestry, European versus African, has a rather substantial effect on what genes are turned on or what genes are turned off in the brain." Weinberger explained that his research predicts the quantitative change in gene activation based on the proportion of European and African ancestry and investigates how that might impact disease prevalence. In a disease-specific example, he explained that Parkinson's disease may be less common among people of African ancestry because of the number of genes that are active or inactive based on the proportion of African ancestry present. Weinberger's research also suggests that the proportion of African ancestry only explains about 30 percent of the probability that someone will develop Alzheimer's disease (AD). Examining biologic material from those with more diverse ancestry may offer opportunities to investigate these theories and "provide insights as to why different ancestry groups vary in their prevalence of some of these diseases and probably also why the biology to some degree varies across populations," Weinberger concluded.

Koroshetz said he has seen conflicting findings on how the misunderstanding of biologic mechanisms can potentially pose medical harm to communities that are underrepresented in research. He explained that people of African ancestry with early state dementia had faced high rates of exclusion from recent anti-amyloid AD treatment trials because their positron emission tomography (PET) scans often did not demonstrate elevated levels of amyloid. This suggests that their dementia has a cause other than AD. "[In addition], the main risk factor for the anti-amyloid therapy [which is used to treat Alzheimer's disease] is leakage and bleeding from a damaged blood vessel," he said. Because African Americans have a predisposition towards hypertension-related damage to the vascular system and there were so few African Americans in the anti-amyloid trials, it is more difficult to counsel African Americans about the risk versus benefit of the new treatment.

Riley said that objective measures could help address these complex challenges. "In thinking about the Alzheimer's [disease] trials, if there was some objective measure of vascular integrity, imagine a world where everyone was simply screened for that measure," she said, "no matter what your ancestry is, if you don't have good vascular integrity, you're in one bucket, and if you have good vascular integrity, you're in another bucket regardless of what your ancestry is." Having objective measures would promote more inclusive practices for the clinical trial recruitment of people from various ancestries in neurological research, she concluded.

Deters suggested that the neuroscience research community think critically about opportunities to be more inclusive in their studies. She recalled a report that Black individuals were more likely to have been excluded from an AD study and that they were less likely to demonstrate elevated amyloid than White individuals (Deters et al., 2021). This caused Deters to wonder if the Black individuals who are participating in these studies are representative of the broader population since they may be more resilient or high performers.

Discussions about increased diversity in research extend beyond racial and ethnic diversity. Wiseman said that cis-gender women, transgender individuals, and non-binary people have also been historically underrepresented in biomedical research, which has

[7] To learn more about the African Ancestry Neuroscience Research Initiative, visit https://aaneuroscienceresearch.com/ (accessed December 4, 2023).

contributed to health disparities and left gaps in research. In response to a question from the audience regarding how to embrace intersectionality and the wide diversity of genetic circumstantial expressions that are determined by life experiences, heritage, and culture, Wiseman suggested using "big data" from biobanks such as the All of Us[8] in the United States and the UK biobank.[9] Admittedly, she added, most of the material in these biobanks comes from more affluent populations, but regardless, these models are a good starting place. She then echoed Riley's point regarding the intention to eventually move away from these proxy measures to start examining more individualized, complex biomarkers.

INCLUDING INDIVIDUALS WITH LIVED/LIVING EXPERIENCE

Phil Gutis, an Alzheimer's Association former early-stage advisor and an individual living with AD, described the need for improved communication between researchers and diverse participants, especially those with lived/living experience. He shared that he was notified of his diagnosis via email, "which basically said, 'Congratulations, you have been diagnosed with early onset Alzheimer's [disease] and are now eligible to participate in the Biogen trial.'" While that may not be standard practice, the email was an example of how the communication to patients can feel unempathetic and dehumanizing, Gutis said. "The other challenge is that when there is generally information about these trials, we're not hearing about it from the researchers or the clinical trials. We're hearing about it, particularly if it's large biopharma, in the media." He said that he had learned that Aducanumab failed its futility test through the news despite being an active participant in the trials. Wiseman added that to build trust with the community, there must be clear and bi-directional communication between researchers and the public. This includes the community sharing their concerns with researchers and researchers clearly articulating clinical results and the short and long-term benefits of research.

Developing a workforce that is more reflective of the communities that have been historically underrepresented in research is essential to building trust and strengthening communication between the research community and those underserved populations, Koroshetz said. He said that NIH is committed to supporting people from underrepresented communities in entering the neuroscience workforce, believing that more diverse perspectives improve the quality of science produced.[10] According to Koroshetz, NIH has developed pipeline programs that support undergraduate through postdoctoral students. But being committed to developing a more diverse workforce is not enough, Koroshetz said, as the responsibility to achieve health equity should not rest solely on those who have been historically underserved, but rather that responsibility should be shared among the entire scientific community.

From a publishing perspective, Wiseman said, "we don't want to see what is sometimes called helicopter science." Journal editors are less interested in seeing researchers drop into communities, extract data, leave, and reap the benefits of the research; she explained, "I would be hesitant to publish a genetic study in a certain population that did not include members of the population as authors." Instead, researchers may consider engaging someone from the community which they are studying as an investigator or build a longer-term, bi-directional relationship with the communities that they are interested in investigating.

Although research has become increasingly diverse and accessible, only a very small percentage of the nation's population is ever involved in research, Koroshetz said. Gutis added, "I hope that we start engaging people with lived experience more broadly through all corridors of research and for all people. There are tons of people who are desperate to engage with the research community, and it would be great if folks were interested in hearing more from us." People living with the diseases being studied rarely hear about the research, and trust is needed to engage those who are aware of the research, Koroshetz responded.

[8] To learn more about the All of Us Research Program's biobank, see https://allofus.nih.gov/funding-and-program-partners/biobank (accessed December 4, 2023).
[9] To learn more about the UK Biobank, see https://www.ukbiobank.ac.uk/ (accessed December 4, 2023).
[10] For more information on the NINDS' health equity recommendations including health disparities training development, see https://www.neurology.org/toc/wnl/101/7_Supplement_1 (accessed January 8, 2024).

THE INTERSECTIONALITY OF CREDIBILITY, INCLUSIVITY, AND EQUITY IN SCIENCE

In summarizing the workshop discussions, Krystal said that they highlighted five important points: the complexity of the study of race versus ancestry, the importance of removing bias from study methods, the opportunity to create partnerships with lived/living experience communities, the importance of having a diverse workforce across all levels, and the opportunity to be intentional about including individuals with lived/living experience and creating systemic change. Trust, engagement, and inclusivity are all required to build credibility with the general public, Krystal said, "and if we want to address the disparities in health that plague our society [and achieve health equity], our science has to become more credible."

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REVIEWERS To ensure that it meets institutional standards for quality and objectivity, this Proceedings of a Workshop—in Brief was reviewed by **Kacie D. Deters,** University of California Los Angeles; **Lilyana Amezcua,** University of Southern California; and **Richard T. Benson,** National Institutes of Health. **Leslie Sim,** National Academies of Sciences, Engineering, and Medicine, served as the review coordinator.

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For additional information regarding the workshop, visit https://www.nationalacademies.org/our-work/mitigating-health-disparities-in-brain-disorders-starting-with-basic-science-a-workshop.

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