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Impact of Cognitive Impairment across Specialties: Summary of a Report from the U13 Conference Series

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Abstract

Although declines in cognitive capacity are assumed to be a characteristic of aging, increasing evidence shows that it is age-related disease, rather than age itself, that causes cognitive impairment. Even so, older age is a primary risk factor for cognitive decline, and with individuals

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Author Contributions:

Authors CC, FM, MA, MB, SI, JK, FL, EM, JM, HW, and SA worked on concept and design of this manuscript. Authors CC, FM, MB, SI, JK, JM, and HW worked on analysis and interpretation of data of the manuscript. Authors CC, FM, MB, SI, JK, FL, EM, DR, RS, HW, SA, and JV worked on the preparation of the manuscript.

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Dedication:

We humbly dedicate this manuscript to Arti Hurria, GEMSSTAR U13 principal investigator, friend, and hero, who lost her life on November 7, 2018. Dr. Hurria was a tireless champion advancing geriatrics concepts across medical specialties. Her exceptional leadership was the driving force behind the successful U13 conferences.

living longer as a result of medical advances, cognitive impairment and dementia are increasing in prevalence. On March 26–27, 2018, the American Geriatrics Society (AGS) convened a conference in Bethesda, Maryland, to explore cognitive impairment across the subspecialties. Bringing together representatives from several subspecialties, this was the third of three conferences, supported by a U13 grant from the National Institute on Aging (NIA), to aid recipients of Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR) in integrating geriatrics into their subspecialties. Scientific sessions focused on the impact of cognitive impairment, sensory contributors, comorbidities, links between delirium and dementia, and issues of informed consent in cognitively impaired populations. Discussions highlighted the complexity not only of cognitive health itself, but also of the bi-directional relationship between cognitive health and the health of other organ systems. Thus, conference participants noted the important of multidisciplinary team science in future aging research. This article summarizes the full conference report, The Impact of Cognitive Impairment Across Specialties and notes areas where GEMSSTAR scholars can contribute to progress as they embark on their careers in aging research.

Introduction

Traditionally, adults are assumed to lose cognitive capacity as they age. However, increasing evidence shows that it is age-related disease, rather than age itself, that causes cognitive impairment. Even so, older age is a primary risk factor for cognitive decline. For example, approximately 10% of individuals aged 65 years and older have Alzheimer's disease (AD)-associated dementia. With medical advances leading to individuals living longer, cognitive impairment and dementia are increasing in prevalence and threaten to become a public health crisis.

Increasing evidence suggests that the pathology underlying AD and other dementias begins long before symptoms appear. For example, 50% of neurons in certain brain regions, such as the hippocampus, are already dead,[1] and other co-pathologies are present by the time the first symptoms of AD appear.[2] Thus, AD can be viewed as a continuous process of synaptic and neuronal deterioration that can be divided roughly into an asymptomatic, preclinical stage, and a symptomatic stage, with the preclinical stage constituting the bulk of the illness. Efforts toward prevention of dementia are under way, and by 2030, there will likely be more preventive options, including risk factor identification and monitoring. Although the transition from the preclinical stage and relative cognitive normality to the initial onset of symptoms is difficult to detect at present, researchers are now characterizing the pre-symptomatic stage. Biomarkers have been identified, including cerebrospinal fluid SNAP-25, VILIP-1, and YKL-40. In addition, race-dependent mechanisms for Alzheimer 's disease are being explored with lower CSF tau noted in African-Americans than in Caucasian participants.[4] Several trials are exploring interventions to prevent or delay the onset of symptoms. Among potential markers of pre-symptomatic illness are physical function and performance. In a longitudinal study of 444 cognitively normal older adults, 134 of whom were later diagnosed with dementia, individuals who later developed dementia did not perform as well as those who remained stable, even when they appeared to be normal.[5]

Despite the promise of these efforts, the only currently available options for management of dementia include managing the disease while caring for the patient, family, and caregivers. Disease management typically relies on the use of cholinesterase inhibitors and memantine, which have only modest benefits.[6] Caring for the patient includes the management of symptoms, which is best addressed by behavioral approaches, and the management of both dementia-related and non-dementia–related comorbidities. New models of comprehensive care focusing both on patients and caregivers, including community-based models such as BRI Care Consultation[7] and MIND at Home[8] and health system-based models such as the multidisciplinary Healthy Aging Brain Center at Indiana University (HABC)[9] and the University of California, Los Angeles Alzheimer's and Dementia Care program,[10] have been shown to reduce caregiver strain and nursing home placements.[7,9–12]

The Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR) award supports early-career physician-scientists and dentist-scientists who have recently completed their medical, surgical, or dental training in any specialty and are launching careers in clinical aging research in that specialty. The program builds on the success of two programs: the T. Franklin Williams Scholar program, previously funded by the Atlantic Philanthropies, and the Dennis W. Jahnigen Scholar program, funded by the John A. Hartford Foundation. On March 26–27, 2018, the American Geriatrics Society (AGS) convened a conference in Bethesda, Maryland, to explore cognitive impairment across the subspecialties. This was the third of three conferences, supported by a U13 grant from the National Institute on Aging (NIA), to aid GEMSSTAR awardees in integrating geriatrics into their subspecialties. Drs. Molly Wagster, of the National Institute on Aging (NIA), Sanjay Asthana, of the University of Wisconsin-Madison School of Medicine and Public Health, and Joe Verghese, of the Albert Einstein College of Medicine, served as Co-Chairs for the meeting. Scientific sessions focused on the impact of cognitive impairment, sensory contributors, comorbidities, links between delirium and dementia, and issues of informed consent in cognitively impaired populations.

As with the previous two conferences in this series, this conference brought together representatives of several subspecialties (Table 1). It aimed to introduce GEMSSTAR awardees to key concepts and approaches to consider and to help them build collaborative networks as they embark on their careers in aging research. This article provides a high-level overview of the full conference report, "The Impact of Cognitive Impairment across Specialties" and notes opportunities for GEMSSTAR awardees to contribute to research progress in this area.

Impact of Cognitive Impairment across Specialties

The conference included a specific focus on the important interrelationship and clinical coexistence between delirium and dementia. Despite exclusive diagnostic criteria that can be distinguished by onset, duration, attention, consciousness, speech, and psychomotor subtypes,[13] one systematic review has found that the presence of dementia at baseline is a strong risk factor for the development of incident delirium and that delirium is a risk factor for subsequent dementia.[14] Another systematic review has shown an association between delirium and increased institutionalization and mortality,[15] and clinical studies have

observed a link between delirium and long-term cognitive decline.[16–18] Thus, the prevention of delirium may offer the unprecedented opportunity to prevent or ameliorate future cognitive decline.

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) definition of delirium is difficult to apply at the bedside, and how to prevent and treat complicated delirium is not clear. Who is at risk, the causes and mechanisms, and the relationships between vulnerability and precipitating factors for complicated delirium, which leads to long-term cognitive decline, are areas of ongoing research. Mechanistic studies in animal models suggest links between anesthesia and surgery and molecular processes associated with AD,[19,20] and changes in AD-associated biomarkers have been associated with increased risk for delirium and postoperative cognitive dysfunction.[21–23] However, whether anesthesia and surgery increases the risk for AD is controversial. A 20-item diagnostic assessment that is based on the Confusion Assessment Method and can be completed in 3 minutes (3D-CAM) has been found to identify patients with delirium, with a sensitivity of 93% and specificity of 96% among normal patients and those with MCI and a sensitivity of 96% and specificity of 86% among patients with dementia,[24] and some items from this assessment can be used as brief screeners.[2253]

Other presentations at the conference discussed several anatomical, neuroimaging, and cerebrospinal fluid biomarkers of AD and noted that changes in some of these biomarkers precede the onset of AD symptoms by at least 20 years.[26] As suggested by a recently published research framework,[2275] the clinical diagnosis of AD will likely be confirmed through measures of amyloid and tau deposition and neurodegeneration. However, this paradigm-shifting framework will have to be confirmed through large, prospective clinical studies before it is adopted for AD diagnosis in clinical practice.

Yet, as one speaker noted, the brain is not an island. Because this conference focused on the impact of cognitive impairment across the medical specialties, an overarching theme was the complex, bi-directional relationship between cognition and other organ systems. A large proportion of intensive care unit (ICU) survivors experience some degree of cognitive impairment upon hospital discharge, and some experience measurable impairment for years afterward.[28] These effects are particularly pronounced among patients aged 65 years and older.[29] Likewise, strong evidence from longitudinal studies indicates associations between sensory impairments, such as olfactory impairment and hearing loss, and cognitive decline and dementia. In fact, a 2017 report from the Lancet Commission concluded that hearing loss was the single modifiable risk factor for dementia, accounting for the greatest proportion of attributable risk compared with all other known modifiable risk factors.[30] Whereas the link between olfactory impairment and cognitive impairment or dementia is likely mediated by a common cause, hearing loss is likely an etiologic contributor to cognitive impairment and dementia. Although some evidence from epidemiological studies suggest an association between visual impairment and cognitive decline and dementia,[31–33] the overall evidence of associations between visual impairments and cognitive decline and dementia is limited and sometimes conflicting.[35–37]

Cognitive impairment can serve as a biomarker of or influence the course of various diseases and conditions. For example, a single-center study in patients with heart failure found that cognitive impairment, as measured by performance on the Mini-Cog, was the strongest independent predictor of a composite outcome of readmission and mortality.[38,39] At the same time, medical comorbidities can affect cognitive health and brain aging. Evidence also suggests that cognitive impairment and a medical condition can have additive or synergistic effects on function. For example, one study has found that the risk for disability is higher with worsening vision loss or cognitive impairment, but that the combination of vision loss and cognitive impairment is associated with even higher risk for disability.[40] Thus, cognitive impairment can therefore be considered as a risk factor or outcome measure for disease. Cognitive impairment may also be a mediator of outcomes, as many aspects of managing medical morbidities, such as taking medications, driving to the doctor's office, and managing diet, depend on cognition. Although it is becoming evident that damage to any organ system affects the brain, the mechanisms underlying this link are not clear. As suggested by one patho-etiologic model of delirium,[41] it is likely that mechanisms differ by organ systems.

Challenges and Strategies in Research on Cognitive Impairment

As noted by conference participants, a major barrier to such research is the exclusion of cognitively impaired patients from studies because of their inability to consent, adhere to protocols, and provide longitudinal outcomes. However, several studies among older adults indicate a high willingness to participate in research in the event that they become impaired and unable to give consent, depending on the risk-benefit profile.[42–46] Safeguards that can protect against unwanted participation include enrollment of impaired individuals only when the research cannot be done as well with individuals who can give consent, enrollment of impaired individuals in research that poses minimal risk or offers a benefit that justifies the risk, the designation of a surrogate decision-maker who can decide based on substituted judgment or the best interests of a participant, and obtaining the impaired patient's assent. Beyond the designation of a legally authorized representative, however, there are no specific guidelines in the federal regulations with respect to these safeguards.

One institutional review board (IRB) suggested that, rather than exclude individuals with dementia, investigators should screen for decisional capacity, with more rigorous and detailed capacity assessments for studies with greater risk, and request an IRB-appointed proxy for those unable to consent.[47] Decision-making capacity includes the ability to communicate a choice, comparative and consequential reasoning, understanding, and appreciation.[48] Although existing assessments of decision-making abilities often ask individuals to make a choice and why they made that choice (e.g., their reasoning), however, they seldom ask about the individuals' understanding or appreciation of a decision. Moreover, tests such as the Mini-Mental State Exam (MMSE), which is copyright-protected, do not offer an adequate assessment of decision-making capacity. How best to assess decisional capacity among patients in the "gray zone," where it is not clear whether an individual is able to give consent, is not clear.

Conference speakers and participants therefore suggested that investigators tailor safeguards to the types of studies they propose to do. Intervention protocols and materials should be adapted for the cognitively impaired, for example by incorporating alternative outcomes that have been adapted for the this population.[47] Corrective feedback and teachback can be used to ensure participants' understanding. Staff who will obtain consent can be trained to conduct assessments of potential study participants' capacity to give consent. Memory aids can be used to emphasize the most important information participants should know about the research being conducted. In one study among patients with AD and a MMSE score of 20 or higher, those who received a one-page summary of key elements at a sixth-grade reading level performed better on understanding and appreciation and were more likely to be judged capable of providing informed consent, compared with those who received a standard consent alone.[49]

The Future of Aging Research: How GEMSSTAR Scholars Can Contribute to Progress

The aging of the U.S. population and the growing burden of dementia make this an area of critical research focus at the NIH. Cognitive impairment and dementia are themselves complex and multifactorial, and as highlighted during this conference, the relationship between cognition and other organ systems is complex and bi-directional. Thus, research exploring mechanisms, methods of identification, prevention, and treatment of cognitive impairment, particularly delirium and dementia, is highly relevant across the medical subspecialties. Likewise, continued research is needed to develop and optimize comprehensive care models focusing on patients with dementia and their caregivers.

Conference participants noted that understanding and addressing cognitive health and its relationship with the health of other organ systems will require multidisciplinary team science. Such teams can approach this complexity by exploring a framework such as the multi-hit model, which describes the theoretical effects of comorbidities on brain structure and function (Figure 1). Or these teams can explore a clinical and scientific problem as a continuum based on an underlying biologic mechanism. Such an approach could draw research questions from problems seen in the clinic and focus on patient-, disease-, care setting-, institution-, and environment-level factors simultaneously. Multidisciplinary team science is the best approach to complex, multifaceted conditions such as cognitive impairment and dementia. Bringing together the right set of collaborators, including individuals on the front lines of the clinical research problem, is important in determining which questions are the most important to study. At Washington University in St. Louis, teams are formed when someone has an idea and the requisite expertise is assembled around that idea. Generating questions from problems seen in clinical care can also add value. In addition, paradigms are shifting, and team science is increasingly recognized as a factor in promotions. Team science also can drive individual members' research into previously unanticipated directions. Thus, it possible to work in multidisciplinary teams and still maintain independence.

Specific research questions discussed at the conference are listed in Table 2. With shifting research, promotion, and tenure paradigms, increasing recognition of the value of team science, and the ability of team science to drive members' individual research projects in unanticipated directions, investigators can participate in multidisciplinary teams and still maintain independence. Thus, GEMSSTAR awardees were encouraged to seek out prospective team members to discuss ideas.

Because the population of older adults and those at risk for cognitive impairment is becoming more diverse, researchers should think proactively of how to develop research questions and study designs that will generate knowledge applicable to a wide range of individuals older than 65 and the experiences they have. Although racial/ethnic gaps in life expectancy have improved from a 13-year gap between white and black individuals in 1900 to a 3-year gap in the present, full equity has not been reached. In addition, the U.S. population is becoming more diverse. Frameworks such as the Centers for Disease Control and Prevention's Health Impact Pyramid and the NIA Health Disparities Research Framework present fundamental factors and levels of analyses to consider when including diverse populations in research. Other mechanisms have also been proposed to explain how sociocultural factors influence behavior and biology.[50,51] The NGAGE model[52] provides a systematic approach to engaging diverse populations in research: Networking, for example by attending community boards and one-on-one leader meetings; Giving first, or building trust by listening to what the community needs; Advocating, or describing the proposed research as trust is built; Giving back, or providing study findings and learning for the community to use once the research is done; and Evaluating how well the study team has done in engaging diverse populations over time.

Several resources are available for junior investigators interested in cognitive research. The NIH TOOLBOX® for Assessment of Behavioral and Neurological Function is a multidimensional set of brief, well-validated, psychometrically sound measures to assess cognitive, sensory, motor, and emotional function across diverse study designs and settings. By using NIH TOOLBOX® measures as an adjunct to their own studies, investigators can facilitate data-sharing and comparison of findings across studies and clinical settings. Investigators also can take advantage of existing datasets (Table 3). However, they should be aware of these databases' limitations, particularly with respect to data on cognition, and tailor their research questions to the amount, type, and quality of available data. Ways to overcome challenges that hamper data-sharing, such as difficulties in managing data-use agreements and IRB-approved consent forms, must also be identified.

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Conflicts of Interests and Disclosures

CC was a speaker for Emergency Medical Abstracts and Best Evidence in Emergency Medicine. CC also serves as a Board Member for Schwartz-Reisman Emergency Medicine Institute International Advisory Board Chair, Deputy Editor-in-Chief Academic Emergency Medicine and Associate Editor Journal of the American Geriatrics Society.

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JM is currently participating in clinical trials of anti-dementia drugs from Eli Lilly and Company and Biogen. JM receives research support from Eli Lilly/Avid Radiopharmaceuticals and is funded by NIH grants # P50AG005681; P01AG003991; P01AG026276 and UF01AG032438.

RS reports grants for clinical research from National Institutes of Health, the Centers for Medicare and Medicaid Services, the Department of Defense, and the Illinois Department of Public Health; being a non-compensated board member of the Alzheimer's Association -- Illinois Chapter; and, being the site principal investigator or sub-investigator for clinical trials for which his institution (Rush University Medical Center) is compensated [Amylyx Pharmaceuticals, Inc., Eli Lilly & Co., Inc., Genentech, Inc., Merck & Co, Inc., Navidea Biopharmaceuticals, Novartis Pharmaceuticals, Inc., Roche Holdings AG, and Takeda Development Center Americas, Inc.].

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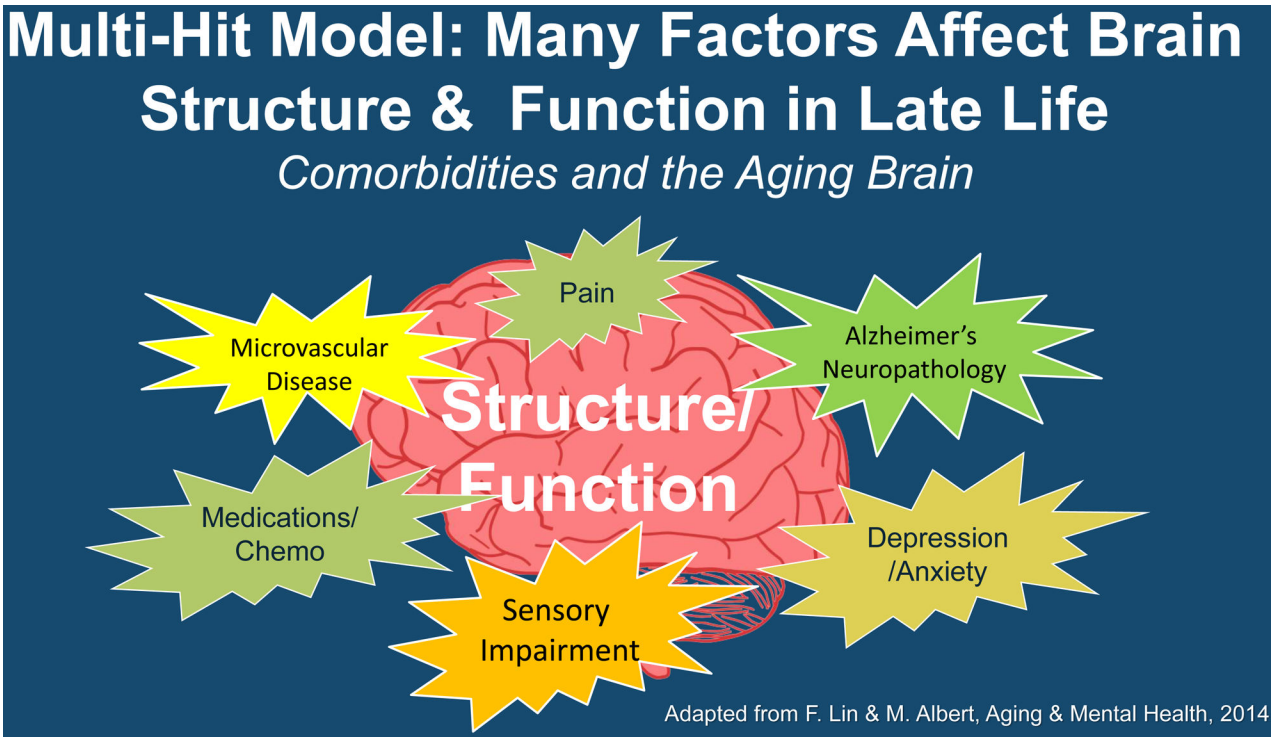

Figure 1:

Multiple co-morbidities affect the cognitive function of the aging brain. Cognitive decline is caused by neurodegenerative diseases, such as Alzheimer's Disease, but other factors that may affect cognitive function in the patient with comorbidities include depression, anxiety, impairments in vision or hearing, medications, cerebrovascular disease, and pain.

Table 1:

Represented Specialties

Anesthesiology	Internal Medicine
Bioethics	Neurology
Cardiology	Oncology
Critical Care	Ophthalmology
Emergency Medicine	Otolaryngology
Family Medicine	Psychology
Geriatric Medicine	

Table 2.

Topics Non-geriatric Subspecialty Researchers Can Explore in Aging Research

Topic	Future Contributions from Specialty Clinician Educators
The bidirectional relationship between cognitive health and the health of other organ systems	• Studies of the role of sensory function as biomarkers of versus contributors to cognitive impairment • Studies of possible synergistic effects between sensory impairments and established risk factors for brain aging, cognitive impairment, and dementia • Development and standardization of neurocognitive testing protocols that account for sensory impairments • Knowledge of how post-ICU trajectories can be modified • Knowledge of how PICS-associated cognitive decline can be distinguished from the trajectory associated with healthy aging • Identification of objective risk factors for post-ICU impairment
Delirium and dementia	• The role of inflammation and neuroinflammation in delirium and dementia • The magnitude by which blood-brain barrier dysfunction in older adults is accelerated after surgery • How disturbances in circadian rhythms mediate delirium and sundowning

Table 3:

Examples of Datasets for Dementia Researchers

Public Datasets	Datasets Used in Psychometrics Conferences
Health and Retirement Study(https://hrs.isr.umich.edu/data-products) National AD Coordinating Center(https://www.alz.washington.edu) AD Neuroimaging Initiative (ADNI) (http://adni.loni.usc.edu/data-samples/access-data)	Rush Religious Orders Study (ROS) https://www.maelstrom-research.org/mica/individual-study/ros#/ and Memory and Aging Project (MAP) https://knightadrc.wustl.edu/Volunteer/MAP.htm Washington Heights Inwood Columbia Aging Project https://www.maelstrom-research.org/mica/individual-study/whicap#/ UC-Davis Diversity Cohort https://health.ucdavis.edu/alzheimers/ Reasons for Geographical and Race Disparities in Stroke (REGARDS) https://www.uab.edu/soph/regardsstudy/ Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) https://clinicaltrials.gov/ct2/show/NCT00298558Framingham Heart Study https://www.framinghamheartstudy.org Adult Changes in Thought (ACT): https://www.maelstrom-research.org/mica/individual-study/act#/ Integrative Analysis of Longitudinal Studies on Aging (IALSA) - https://www.maelstrom-research.org/mica/network/ialsa#/