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The Impact of Cognitive Impairment Across Specialties: A Report from the U13 Conference Series

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EXECUTIVE SUMMARY

On March 26-27, 2018, the American Geriatrics Society convened the third of three conferences, supported by a U13 grant from the National Institute on Aging (NIA), to aid Grants for Early Medical/Surgical Specialists Transition to Aging Research (GEMSSTAR) awardees in integrating geriatrics into their subspecialties. This conference focused specifically on cognitive impairment. Drs. Molly Wagster, of NIA, Sanjay Asthana, of the University of Wisconsin-Madison, and Joe Verghese, of the Albert Einstein College of Medicine, served as meeting Co-Chairs.

Following introductory remarks by Dr. Arti Hurria, Principal Investigator of the GEMSSTAR U13, and meeting Co-Chairs, the meeting on cognitive impairment began with two keynote presentations. The first was an overview by Dr. John Morris, of the Washington University in St. Louis, on the impact of cognitive impairment. Dr. Morris discussed the potential economic impact of an aging society, the public health impact of age-related cognitive impairment and dementia, and the current state of research in Alzheimer's disease. The second was a presentation from Dr. David Reuben, of the David Geffen School of Medicine at UCLA, who reviewed clinical implications of cognitive impairment in daily practice and models of more patient- and family-centric collaborative care with respect to cognitive impairment. Dr. Reuben emphasized the need for caregiver support and presented feasible models to provide comprehensive care that focuses on both the patient and the vulnerable caregiver.

The first scientific session explored cognitive impairment in the subspecialties. Dr. Frank Lin, of the Johns Hopkins University schools of medicine and public health, discussed sensory impairments as biomarkers of and/or etiologic contributors to cognitive impairment and dementia. Dr. Heather Whitson, of the Duke University Medical Center and Durham VA GRECC, described the bidirectional relationship between cognitive impairment and medical comorbidities. Dr. Michael Avidan, of Washington University in St. Louis, discussed the link between critical illness and possibly preventable cognitive impairment. All three speakers pointed out that the severity of cognitive impairment or the rate of cognitive decline might be alleviated by intervening upon different aspects of health. Discussion focused on the complexity surrounding the role of cognition in different health states, and speakers suggested approaching both the problem as a mechanism-based continuum and the research itself as a continuum from cellular animal models through translation to clinical research. Multidisciplinary teams centered around these continuums were discussed specifically.

The second scientific session focused on informed consent for the cognitively impaired. Dr. Jason

Karlawish, of the University of Pennsylvania, discussed how to assess an individual's capacity for informed consent. Dr. Dave Wendler, of the National Institutes of Health Clinical Center, described the ethical considerations of research in cognitively impaired patients. Dr. Wendler also outlined safeguards to prevent unwanted participation in research. Dr. Christopher Carpenter, of the Washington University in St. Louis, described a paper in which an institutional review board suggested solutions to address individuals' inability to consent, adhere to protocols, and provide longitudinal outcomes. Discussion focused on ways memory aids can aid participants in navigating the dense and technical language in consents, concerns about self-stigmatization among individuals who may or may not be able to provide consent, and the need to alert clinical care teams if individuals are identified with clinically significant cognitive impairment.

The third scientific session focused on delirium and dementia. Dr. Sharon Inouye, of Hebrew Senior Life, Beth Israel Deaconess Medical Center, and Harvard Medical School, discussed epidemiologic, clinical-pathologic, and mechanistic studies exploring the interface between delirium and dementia. Dr. Asthana described imaging and cerebrospinal fluid biomarkers associated with dementia, and Dr. Edward Marcantonio, of Beth Israel Deaconess Medical Center and Harvard Medical School, discussed a shorter diagnostic tool for and inflammatory biomarkers associated with delirium. Dr. Miles Berger, of the Duke Centers for Aging and Cognitive Neuroscience and the Duke Anesthesiology Department, discussed delirium versus post-operative cognitive dysfunction and a study exploring correlations between perioperative changes in Alzheimer's disease cerebrospinal fluid biomarkers and longer-term changes in cognition. Discussion focused on the burden of delirium, controversy around recognition of and screening for delirium, and the potential role for inflammation in delirium and long-term postoperative cognitive decline.

The meeting also included a session on resources for junior investigators. Dr. Wagster provided an introduction of the NIH Toolbox for Assessment of Behavioral and Neurological Function. Dr. Raj C. Shah, of Rush University Medical Center, discussed the need for including diverse populations and ways to engage such populations in research. Dr. Dan Mungas, of the University of California, Davis, discussed challenges in data-sharing and provided examples of datasets relevant to cognition and aging. Discussion focused on using the NIH Toolbox as a multidimensional set of brief measures to assess cognitive, sensory, motor, and emotional functions across diverse study designs and settings. In addition, discussion focused on the inclusion of racial and ethnic minorities in research.

Dr. Robin Barr provided a brief presentation on NIA research directions. The meeting closed with a keynote from Dr. Inouye on lessons learned during her career.

Discussion Themes from the Conference

- Understanding the mechanisms, methods of identification, prevention, and treatment of cognitive impairment (delirium and dementia) is a critical area of research with pertinence to the subspecialties.

- Multidisciplinary teams can be centered around understanding the mechanism underlying the role of cognition in a health state and where specific research questions fall on that continuum. Teams can also be built around a research continuum itself, from mechanistic research through translation to interventional research.

- Assessing potential participants' ability to consent to research is an ethical obligation. Safeguards to prevent unwanted participation in research should be tailored to the study.

- The NIH Toolbox for Assessment of Behavioral and Neurological Function is designed for investigators to use as an adjunct to their studies. Incorporation of these measures can provide some uniformity of measures across studies.

- The population of older adults and those at risk for cognitive impairment is becoming more diverse. Thus, researchers should think proactively of how to develop research questions and study designs that will generate knowledge applicable to diverse older adult populations.

- New models of comprehensive care that focuses on patients with dementia and their caregivers are available and should be disseminated. Continued research on developing and optimizing models of care for this vulnerable population are needed.

- The aging of the U.S. population and the growing burden of dementia makes this an area of critical research focus at the NIH.

- Several resources are available for junior investigators interested in cognitive research including the NIH toolbox and public datasets to utilize in cognitive aging research.

ABBREVIATIONS

Aβ	amyloid beta
AD	Alzheimer's disease
ADRC	Alzheimer's Disease Research Center
ADL	activity of daily living
AGS	American Geriatrics Society
CAM	Confusion Assessment Method
CNS	central nervous system
CSF	cerebrospinal fluid
DIAN	Dominantly Inherited Alzheimer's Network
EHR	electronic health record
FOA	funding opportunity announcement
GEMSSTAR	Grants for Early Medical/Surgical Specialists Transition to Aging Research
HABC	Healthy Aging Brain Center at Indiana University
ICU	intensive care unit
IRB	institutional review board
MADCO-PC	Markers of Alzheimer's Disease and Neurocognitive Outcomes after Perioperative Care
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA	National Institute on Aging
PET	positron emission tomography
PICS	post-intensive care syndrome
POCD	postoperative cognitive dysfunction or decline
RCT	randomized controlled trial
SAGES	Successful Aging after Elective Surgery

DISCUSSANT PROFILES

Discussant	Specialty	Affiliation	Expertise	Lab Home
Sanjay Asthana, MD	Geriatrics	University of Wisconsin	Neuro-endocrinology and dementia	http://www.medicine.wisc.edu/people-search/people/staff/402/Asthana_Sanjay
Michael Avidan, MBBCh	Anesthesiology Critical Care	Washington University in St. Louis	Post-operative outcomes, including delirium	http://anest.wustl.edu/faculty/avidan_michael
Robin Barr, DPhil	Psychology	National Institute on Aging	Young investigator development	https://www.nia.nih.gov/about/staff/barr-robin
Miles Berger, MD, PhD	Anesthesiology	Duke University	Post-operative cognitive dysfunction Delirium	https://dibs.duke.edu/scholars/miles-berger
Christopher Carpenter, MD, MSc	Emergency Medicine	Washington University in St. Louis	Implementation Diagnostics Guidelines	http://emed.wustl.edu/Research/Chris-Carpenter-Bio/Christopher-Carpenter-Lab
Arti Hurria, MD	Geriatrics Oncology	City of Hope	Cancer outcomes Mentorship	https://vimeo.com/256613609
Sharon Inouye, MD, MPH	Geriatrics	Harvard Medical School	Delirium Functional decline	https://www.marcusinstituteforaging.org/scientists/team-profiles-and-bios/sharon-k-inouye-md-mph
Jason Karlawish, MD	Geriatrics	University of Pennsylvania	Research ethics in dementia Health policy	https://pennmemorycenter.org/who-we-are/staff/jason-karlawish-md/
Frank Lin, MD, PhD	Otolaryngology	Johns Hopkins University	Sensory impairment Dementia	http://www.linresearch.org
Edward Marcantonio, MD, SM	Geriatrics	Harvard Medical School	Delirium recognition and biomarkers Clinical epidemiology Outcomes of hospitalization and surgery	https://connects.catalyst.harvard.edu/Profiles/display/Person/3871
John Morris, MD	Neurology	Washington University in St. Louis	Alzheimer's dementia	https://hopecenter.wustl.edu/?faculty=john-morris-md
Dan Mungas, PhD	Neurology	University of California-Davis	Alzheimer's dementia	https://health.ucdavis.edu/neurology/faculty/mungas.html

DISCUSSANT PROFILES /cont.

Discussant	Specialty	Affiliation	Expertise	Lab Home
David Reuben, MD	Geriatrics Internal Medicine	UCLA	Frailty Cognitive impairment Dementia	https://www.uclahealth.org/david-reuben
Raj Shah, MD	Family Medicine	Rush University Medical Center	Community-based research	https://www.rushu.rush.edu/faculty/raj-c-shah-md
Joe Verghese, MBBS	Geriatrics	Albert Einstein College of Medicine	Mobility and cognitive impairment	http://www.einstein.yu.edu/faculty/5323/joe-verghese/
Molly Wagster, PhD, MS	Behavioral and Systems Neuroscience	National Institute on Aging	NIH Toolbox	https://www.nia.nih.gov/about/staff/wagster-molly
Dave Wendler, PhD, MA	Philosophy Bioethics	National Institutes of Health Clinical Center	Research ethics Informed consent Vulnerable populations	https://www.bioethics.nih.gov/people/wendler-bio.shtml
Heather Whitson, MD	Geriatrics Ophthalmology	Duke University School of Medicine	Vision and cognitive decline	https://medicine.duke.edu/faculty/heather-elizabeth-whitson-md
Sue Zieman, MD, PhD	Cardiology Geriatrics	National Institute on Aging	Integrating aging research and geriatrics into the medical and surgical specialties Young investigator development	https://www.nia.nih.gov/about/staff/zieman-susan

INTRODUCTION AND OVERVIEW

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 Grants for Early Medical/Surgical Specialists Transition to Aging Research (GEMSSTAR) awardees in integrating geriatrics into their subspecialties. Drs. Molly Wagster, of the 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.

The conference emphasized networking and mentoring. GEMSSTAR awardees participated in small-group sessions to practice and refine their research pitches; engaged in a networking session with program officers, mentors, and scholars from the National Institutes of Health (NIH); presented their work during a poster session; and heard talks from senior investigators and NIH staff on aspects of career development and resources for junior investigators. In keeping with the overall topic of the conference, however, GEMSSTAR awardees also heard talks on the impact of cognitive impairment, clinical implications in daily practice and models of care, informed consent for the cognitively impaired, and cutting-edge research on delirium and dementia. This report summarizes the scientific presentations of the meeting.

THE IMPACT OF COGNITIVE IMPAIRMENT: AN OVERVIEW

John Morris, MD
Washington University in St. Louis

Medical advances have contributed to increasing lifespans. This, combined with declining birthrates, means that the U.S. population is aging. This will have enormous economic repercussions. Cognitive impairment and dementia, which are associated with older age, will become a public health crisis as well.

It has been assumed, that individuals lose cognitive capacity as they age. However, evidence clearly shows that it is not age, but age-related disease, that causes cognitive impairment; aging alone allows individuals to remain healthy and independent. In a longitudinal study of 444 cognitively normal older adults, 134 were later diagnosed with dementia.[1] The rest remained unimpaired throughout the 10-year follow-up period. Further study showed that even at a time when they appeared to be normal, individuals who later developed dementia already did not perform as well as those who remained stable.

For this conference, dementia is defined as an acquired syndrome of decline in memory and other cognitive domains sufficient to affect daily function. It can arise from any disorder that damages higher-order brain regions affecting cognition, and it is often a multifactorial problem. Although Alzheimer's disease (AD) has been the primary focus in discussions of dementia and age-associated

neurocognitive disorders, there are several other neurodegenerative and acquired causes. Detection of dementia depends on intra-individual declines in previously established cognitive and functional abilities, not on comparisons of cognitive test performance between the affected individual and that of age- and education-matched controls.

Although older age does not necessarily lead to cognitive decline, it is a primary risk factor. Approximately 10% of individuals aged 65 years and older have AD-associated dementia. About two-thirds of these individuals are women, and African American and Hispanic individuals are at increased risk. Eighty-five percent of these patients are cared for by family caregivers, not skilled nursing facilities as generally believed. The Alzheimer's Association estimates that caring for individuals with AD dementia costs a total of $277 billion in direct costs, $186 billion of that in Medicare or Medicaid payments.

AD can be viewed as a brain disorder, regardless of the individuals' clinical status. It is a continuous process of synaptic and neuronal deterioration that can be divided roughly into an asymptomatic, preclinical stage and a symptomatic stage. The transition from the preclinical stage and relative cognitive normality to the initial onset of symptoms is difficult to detect, but the symptomatic stage clearly progresses. At mild stages, individuals with AD dementia have clear cognitive deficits, but look and behave normally and participate in their communities. At severe stages, they no longer recognize family members, and they require full care to manage activities of daily living (ADLs).

Of all the major killers, AD is the only one for which there are no effective therapies or preventive interventions. Since 2001, all clinical trials of potential therapies, most of which target amyloid beta (Aβ), have failed.[2] The reasons for these failures are not clear, but some have suggested that these therapies were ineffective in general or addressed the wrong biologic target.[2] All these trials tested therapeutics as monotherapies, when dementia is known to have multifactorial causes. These trials might have initiated therapies at too late a time in AD progression. By the time the first symptoms appear, 50% of neurons in certain brain regions, such as the hippocampus, are already dead,[3] and other copathologies are present.[4]

Researchers are now characterizing the pre-symptomatic stage, which appears to represent the bulk of the illness. Biomarkers have been identified, and several trials are exploring interventions to prevent or delay the onset of symptoms. NIA is supporting a wide array of research, for example at the Knight Alzheimer's Disease Research Center (ADRC) at Washington University in St. Louis. One NIA grant supports the development of the international Dominantly Inherited Alzheimer Network (DIAN), whereas others assess the more common late-onset sporadic form of AD and potential biomarkers of the preclinical stage. The Knight ADRC collaborates with other institutes across the United States and around the world. For example, the ADRC collaborates with DIAN and the Alzheimer's Disease Centers. The Knight ADRC also emphasizes multidisciplinary research,[5] such as work showing that non-cardiac surgery does not affect cognition in older adults[6] and that dementia is often unrecognized in emergency departments.[7] This follows the NIA's push toward multidisciplinary research,

illustrated by several funding opportunity announcements (FOAs).

There have been remarkable advances in AD, but understanding of this complex disease is still incomplete. Multi- or interdisciplinary approaches will be needed to solve its complexities and develop effective preventive interventions and treatment.

Clinical Implications in Daily Practice and Models of Care

David Reuben, MD
David Geffen School of Medicine, UCLA

The natural history of dementia encompasses a progressive cognitive decline (e.g., 3 to 4 points per year on the Mini-Mental State Examination [MMSE]),[8] as well as emergence of non-cognitive symptoms such as psychosis (20% of patients), depressive symptoms (40% of patients), and agitation or aggression (80% of patients). Survival among patients with AD is about 3 to 12 years following symptom onset; other dementias are associated with worse survival primarily because of associated comorbidities. Stages of dementia are defined by declining cognitve scores and by increasing or more severe functional impairments, cognitive changes, behavioral issues, and complications.

Prevention efforts are under way, and by 2030, there will likely be more preventive options, including risk factor identification and monitoring. At present, however, the only options for management of dementia include managing the disease and caring for the patient. The disease is typically managed with cholinesterase inhibitors and memantine. These options have modest benefits, however; they might change the trajectory of dementia, but they do not reverse it.[9] Caring for the patient centers around achieving the highest level of independence that works for everyone involved. Several issues must be addressed, such as driving and living alone, management of symptoms and comorbidities, and advanced care planning. Behavioral approaches tend to work best for symptom management; available drugs, such as antipsychotics, have side effects and are associated with cardiovascular mortality. Management of comorbidities encompasses dementia-related comorbidities, such as falls, immobility, and incontinence, and non-dementia–related comorbidities such as aging-related diseases and issues of adherence and competing priorities. The ability to include the patient in decision making also depends on where the patient is in disease progression. At early stages, the patient can be included in decision-making, but at later stages, family members and caregivers will play a larger role.

Caregivers are the most important resources for patients with dementia, and more than half of them develop depression. The more empowered and knowledgeable they are, the better care they can provide for patients. Thus, caregiver support is critical. Support is available from health care systems, community organizations such as the Alzheimer's Association, and specific programs like REACH, Partnering With Your Doctor, and Savvy Caregiver. More than 200 interventions, including care coordination, behavioral management, counseling and psychotherapy, and skills training, have been assessed in randomized controlled trials (RCTs).[10] Although most of these resources are effective, the benefits are moderate. They focus only on

the caregiver and integrate poorly with health care systems, and they have been tested by traditional research methods and not pragmatic trials. In addition, the costs of these programs are not adequately reimbursed by Medicare and other insurers.

New models of comprehensive care that focus both on patients and caregivers have been developed. Community-based models such as BRI Care Consultation[11] and MIND at Home[12] provide systematic assessments, care planning, care delivery or referrals, and support. They have been shown to reduce caregiver strain and nursing home placement and to provide better care options, but have no effect on health care utilization or costs.[11,13,14] Health system-based models such as the Healthy Aging Brain Center at Indiana University (HABC) focus on improving self-management, problem-solving, and coping skills. HABC emphasizes a multidisciplinary care team that relies on community health workers as the front-line liaisons between the care team and the patients and their caregivers. Compared with usual primary care, HABC has reduced health care utilization as demonstrated by fewer emergency room visits and hospitalizations and reduced length of stay.[15] Likewise, the University of California, Los Angeles (UCLA) Alzheimer's and Dementia Care (ADC) program[16] approaches the patient and caregiver as a dyad in which both need support and provides comprehensive care through assessments, individualized care plans, round-the-clock access to support, and partnerships with community resources that provides direct resources to patients and families and trains family and caregivers. The UCLA ADC program has reduced behavioral symptoms, depression among patients, and caregiver distress. It also has resulted in reduced nursing home placements and lowered annual Medicare costs.

Cognitive Impairment in the Subspecialties Sensory Contributors to Cognitive Impairment

Frank Lin, MD, PhD
Johns Hopkins School of Medicine and Bloomberg School of Public Health

The senses serve as the only way that the brain interacts with the world and thus are the mediators of individuals' experiences. Yet how the senses modify or influence the brain is often ignored. In assessing potential associations between sensory and cognitive impairment, it is important to remember that each sensory system is distinct in terms of embryonic origin, transduction processes, and mechanisms of peripheral-central and neural processing. Each system must therefore be considered distinct in how it may interact with and affect cognition. In addition, measurements of sensory function reflect different levels of function, varying from purely peripheral to more central measures of sensory function. Thus, each measure reflects a different underlying construct, which in turn affects scientific interpretations of results.

Unlike other senses, olfaction is a direct projection of the central nervous system (CNS). According to data from the National Social Life and Aging Project, almost all individuals in their late 50s can identify at least three of five odors, but this ability declines with older age.[17,18] Strong evidence from longitudinal studies suggests that impairments in odor identification is associated with cognitive decline, incidence dementia, and AD biomarkers and pathology. It is likely that the

connection between olfactory impairment and cognitive impairment or dementia is mediated by a common cause, for example AD-associated pathology and neurodegeneration.

Hearing encompasses both peripheral and central components. Sounds are transduced by the peripheral auditory system, or the cochlea, which converts the auditory signal into a neural signal that travels to the auditory cortex for decoding. "Hearing loss" is generally understood to mean impairments in the peripheral auditory system (measured with audiometric tests) and is highly prevalent in older adults: approximately two-thirds of individuals aged 70 or older have a clinically significant hearing impairment.[19] Relatively strong evidence from longitudinal studies has associated peripheral hearing loss with cognitive decline and incident all-cause dementia, and 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.[20] Unlike olfaction, hearing loss is likely an etiologic contributor to cognitive impairment and dementia. It may contribute to cognitive impairment through cognitive load, through changes in brain structure, and/or social isolation. General confounders in the association between hearing loss and cognitive impairment include age, education, and cardiovascular risk factors.

Like hearing, our sense of vision is dependent on both peripheral transduction and central processing of the visual image. Through the late 70s, only 10% of individuals have visual impairments that cannot be corrected to at least 20/40. That prevalence increases substantially among individuals in their 80s.[21] The evidence of associations between visual impairments and cognitive decline and dementia is limited and sometimes conflicting.[22-25] However, there is some evidence from cross-sectional studies of such an association.[26-28] Further research is needed to characterize the degree to which visual impairments may mechanistically contribute to impaired cognition (e.g., through effects of visual impairment on social isolation, brain structural changes) versus impairments in visual/retinal function reflecting common neuropathologic etiologies that also contribute to cognitive impairment.

Neuropsychometric testing could be confounded by sensory function. For example, test results will be biased if someone with a hearing loss cannot hear instructions or misunderstands spoken auditory stimuli (possible in cases of severe hearing loss), or a patient with visual impairment is unable to read instructions. Yet there are no broadly applicable protocols or established standards to address sensory impairment in cognitive testing, and individuals with sensory impairments may often be excluded from neurocognitive studies. In contrast, some measures of sensory testing could also be confounded by cognitive function. If a patient performs poorly on odor identification, it is not clear whether such a result reflects actual olfactory impairment versus an impairment in recalling and naming the odorant.

More work is needed to understand the role of sensory function as biomarkers of versus contributors to cognitive impairment. Studies are also needed to assess possible synergistic effects of sensory impairments with other established

risk factors for brain aging, cognitive impairment, and dementia. Neurocognitive testing protocols that account for sensory impairments should be standardized and disseminated.

Two-Way Street: Comorbidities and the Aging Brain

Heather Whitson, MD
Duke University Medical Center and Durham VA GRECC

Cognitive impairment is associated with medical comorbidities in a bidirectional manner: cognitive health affects the course of many diseases, and at the same time, medical comorbidities affect cognitive health and brain aging. Cognitive impairment can therefore be considered as a risk factor or outcome measure for disease. 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.[29,30] When considering cognitive performance as a risk factor, however, one should note that performance on cognitive assessments can be affected by sensory impairment, socioeconomic status, education level, race or ethnicity, and sex.

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. Cognitive impairment combined with a medical condition can have an additive or synergistic effect 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.[31]

Cognitive impairment can be identified in this context by administering a validated cognitive screen as part of care for other medical conditions. Strategies to assist cognitively impaired individuals include providing take-home materials and appropriate referrals, reducing learning objectives, and engaging caregivers. Caregiver engagement is particularly important, as demonstrated by a pilot study of low vision rehabilitation among patients with mild cognitive impairment (MCI).[32] This study also found that by the end of the 6-week intervention, two-thirds of the patients had experienced significant life events such as hospitalizations. Regardless of medical subspecialty, cognitive impairment is likely to be prevalent in the patient population, and the combination of cognitive impairment and medical comorbidity adds substantial complexity. A theoretical model suggests that the aging brain receives multiple hits from AD or other neuropathology, microvascular disease, sensory impairments, depression or anxiety, pain, and medications and that these multiple hits contribute to the high rates of cognitive impairment in multimorbid populations.

No Brain Is an Island

Michael Avidan, MD
Washington University in St. Louis

Up to 9 of 10 survivors of the intensive care unit (ICU) will experience some degree of cognitive impairment upon hospital discharge, and approximately half of those survivors

will experience measurable impairment for years afterward.[33] Although these effects are apparent across the age spectrum, they are more marked among patients aged 65 years and older.[34] Impairments are apparent in several domains, including executive function, memory, attentional function, and processing speed,[35] and they are associated with other neurologic and neuropsychiatric disorders, including depression, posttraumatic stress disorder, pain, and anxiety. For example, a study by Duggan and colleagues found that patients with executive dysfunction at 3 months were more likely to be depressed 12 months later.[36]

The high likelihood of cognitive impairment among ICU survivors suggests that damage to any organ system affects the brain. However, the mechanisms underlying this link are not clear. As suggested by one patho-etiologic model of delirium,[37] it is likely that the relationship is a complex one, with mechanisms differing by organ systems. The prevailing narrative suggests that several factors give rise to the cognitive, mental, and physical impairments seen with post-intensive care syndrome (PICS).[38] This narrative also suggests that implementing a bundle of interventions, including awakening using light or minimal sedation, spontaneous breathing trials, coordination of care and communication among various disciplines, delirium monitoring and management, and early ambulation, will alleviate not only PICS-associated delirium but also long-term cognitive decline. More work is needed to determine how to modify post-ICU trajectories and how to distinguish PICS-associated cognitive decline from the trajectory associated with healthy aging.

Cognitively damaging aspects of critical illness can include risk factors, factors arising from medications and the ICU environment, factors related to the patient's immunologic and inflammatory response, and long-term sequelae.[35,39,40] For example, mechanical ventilation exerts deleterious effects on the brain through several mechanisms involving neural, inflammatory, immunologic, and neuroendocrine pathways.[35] Thus, strategies that minimize lung stretch might have long-term cognitive benefits.

Identifying objective risk factors is the first step toward developing and targeting interventions to prevent post-ICU impairment.[33] For example, a study demonstrating the prevalence of sleep abnormalities following critical illness and a longitudinal association between these abnormalities and cognitive impairment would provide potential therapeutic targets and clinical endpoints for ICU-based studies.[33] Likewise, post-ICU electroencephalography might show features suggesting specific cognitive impairments.[33] In yet another example, the microbiome is emerging as an essential organ system, and animal studies have shown that changes to the microbiome induces behavioral changes suggestive of cognitive and neurologic impairment.[41] Approximately 60% of available medications affect the human microbiome.

Cognitive Impairment in the Subspecialties: Discussion

An overarching theme in this session is the complex, bidirectional relationship between other organ systems and cognition. Cognitive impairment can serve as a biomarker of or affect the course of various diseases. At the same time,

medical conditions can also influence cognitive health. Thus, care for other conditions, including sensory loss, should account for cognitive impairment.

The complexity of this relationship is best visualized by conceptual frameworks, which can vary based on the health state of interest. For example, vision loss and cognitive impairment can have a common cause, or they may influence each other (Figure 1).

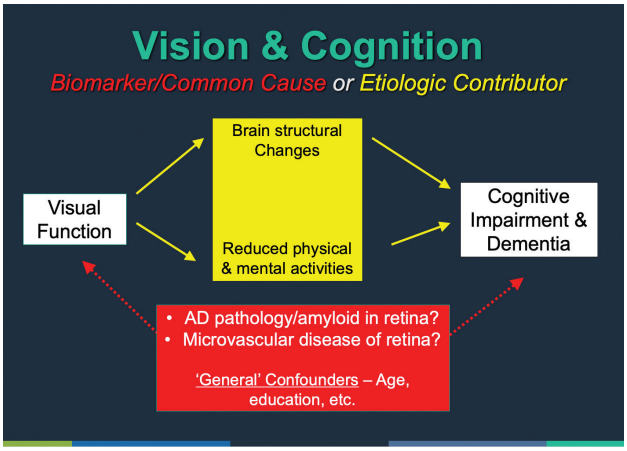

Figure 1. Potential relationships between vision loss and cognitive impairment. (Lin presentation slide 14)

Another example is the theoretical multi-hit model describing the effects of comorbidities on brain structure and function (Figure 2).

Another approach involves the consideration of a problem as a continuum based on a mechanism that draws patient-, disease-, care setting-, institution-, and environment-level factors together. For example, the relationship between critical illness and cognitive impairment can be influenced by patient factors, systemic insults, and factors related to the ICU, among others (Figure 3).

In addition, the research itself is a continuum,

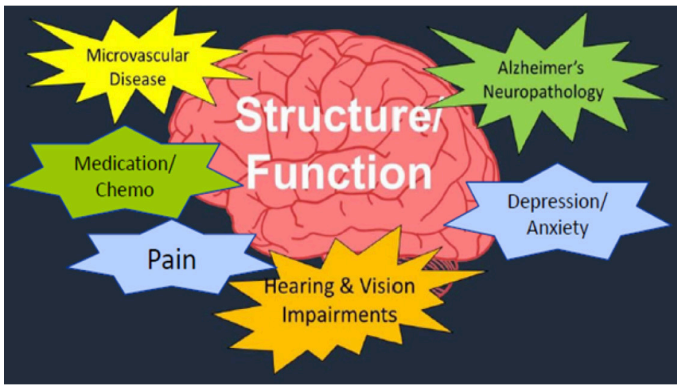

Figure 2. Theoretical "multi-hit" model of the relationship between comorbidities and cognition. (Whitson presentation slide 12)

from cellular and animal models through translation to clinical studies, and the translational stages are often missed. In this context, investigators will not have to choose whether to focus purely on mechanisms or interventions; they can focus on both. However, it should be noted that working in both realms is difficult to do quickly.

Multidisciplinary team science can be centered around such a continuum and 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 is

possible to work in multidisciplinary teams and still maintain independence. New and early-stage investigators are encouraged to seek others out to discuss ideas, and they should be persistent in seeking face-to-face meetings.

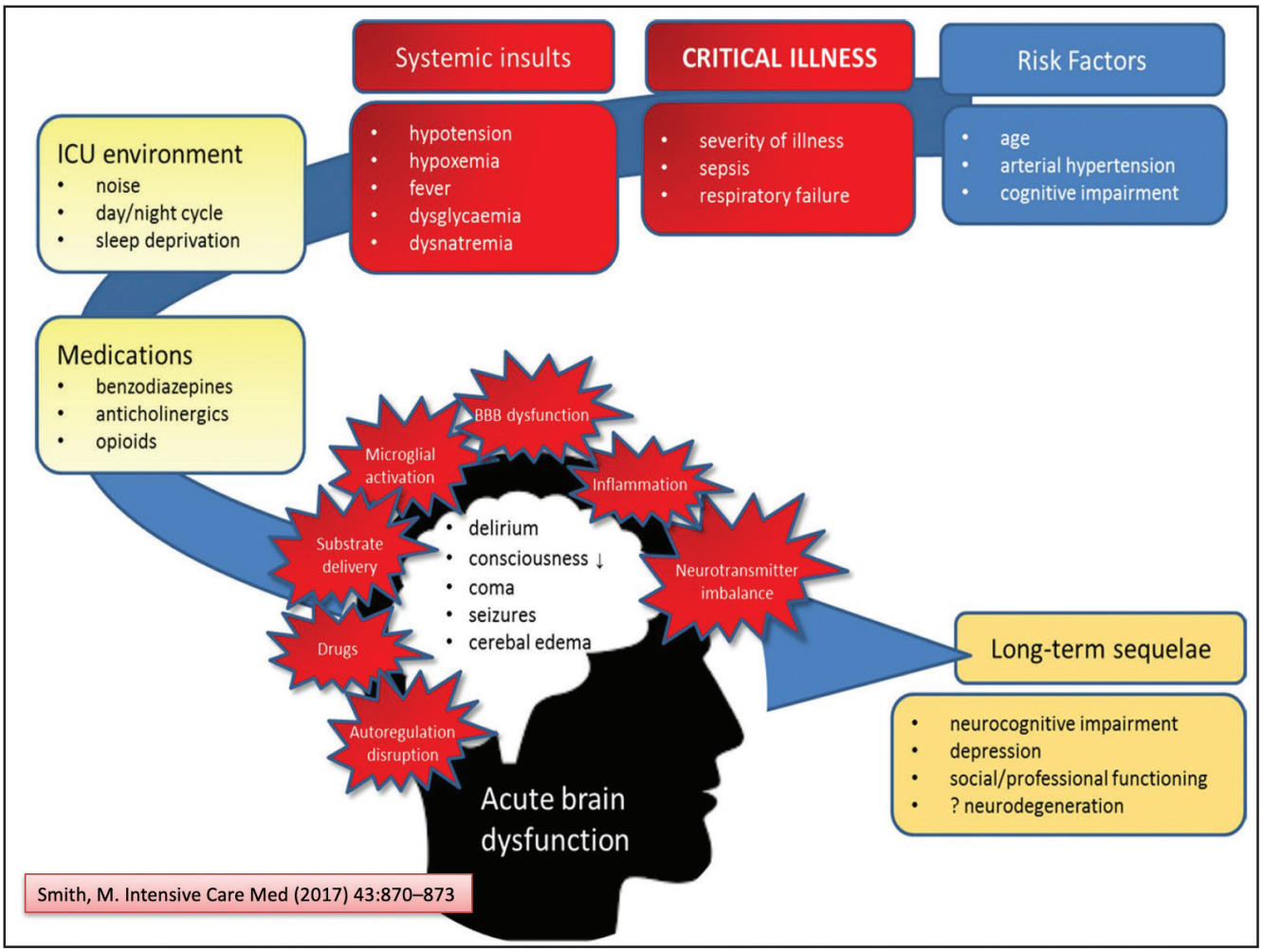

Figure 3. A continuum of factors influencing the relationship between critical illness and cognitive impairment. (Avidan presentation slide 11)

INFORMED CONSENT FOR THE COGNITIVELY IMPAIRED

How to Assess Capacity to Consent

Jason Karlawish, MD
University of Pennsylvania

To assess a person's capacity to consent, we assess their decisional abilities, also called decision-making abilities. These abilities include communicating a choice, comparative and consequential reasoning, understanding, and appreciation.[42] An individual's capacity to make a decision, such as whether to participate in a study, reflects in part how she performs along the continuum of the decision-making abilities. The decision that an individual lacks adequate capacity depends on the assessor's judgment of individual performance on the decisional abilities the assessor chooses to assess.

These abilities are driven by, but are not the same as, overall cognition, which encompasses several domains, including memory and executive function. The MMSE is not an adequate assessment of decision-making capacity. An individual with an MMSE score as low as 8 can express a choice, but a study that sets that as a standard will enroll several individuals who cannot understand or appreciate what they are participating in. Teasing out the ability to understand and appreciate provides substantial clinical information and a better representation of a person's decisional capacity.

The ability to understand is defined as the ability to know facts. This can be assessed, for example, by explaining the risks of a research study, then asking the person to describe the risks in his or her own words. The ability to appreciate is defined as individuals' ability to apply the facts to her life. This requires individuals to assign values to the information they have been given and to make a judgment about why a fact, such as risk, could happen to them. This can be assessed, for example, by asking the person what she sees as the benefits or risks to her of participating in a study. Although 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. An individual's answers to a question assessing one decisional ability might mix her performance on other abilities as well. For example, if an individual is told that one risk of the study drug is blood loss, that individual might simply say, "You mean I might become anemic and get weak," an answer that shows both understanding (anemic) and appreciation (get weak).

In one study to improve decision-making ability, patients with AD dementia and a MMSE score of 20 or higher were randomized to a standard consent or a standard consent plus a memory aid, a one-page summary of key elements at a sixth-grade reading level.[43] Individuals who received the memory aid performed better on understanding and appreciation and were more likely to be judged capable of providing informed consent. Conducting such an intervention can also provide measures of decisional ability. Thus, investigators should select the key facts research participants need

to understand and appreciate to participate in a study. Studies with greater risk should have more rigorous and detailed capacity assessments.

Conducting Ethical Research with Adults Who Cannot Consent

Dave Wendler, PhD, MA
National Institutes of Health Clinical Center

Several studies have assessed individuals' willingness to participate in research should they become impaired and unable to give consent. A study of individuals at risk for AD found a high willingness to participate, even in research that would not offer a potential benefit to the participants themselves.[44] In another study in the NIH Clinical Center, where participants could indicate their willingness on advance directives, about 49% were willing to participate in minimal-risk research that would not help them, 13% were unwilling to participate in research at all if they were unable to give consent, and 9% were willing to participate in research that would not help them and is greater-than-minimal risk.[45] In a study of more than 1,500 older Americans, about 71% were willing to participate in non-beneficial studies involving lumbar puncture, and almost 80% were willing to participate in a potentially beneficial drug trial.[46] However, the level of willingness tracked with the potential for benefit. Only 57.4% in that study were willing to participate in a vaccine trial.[46] Focus groups of older adults have shown fairly strong support and a willingness to participate in research, but participants were aware of the potential for abuse and stressed that risks should be limited.[47] Another study found that many individuals were willing to participate in research if they became impaired, and they supported the use of surrogates, but their willingness decreased as the risk-benefit profile became less favorable.[48] Thus, enrollment decisions must account specifically for individual preferences and values.

One safeguard that can help realize this type of protection is a necessity requirement. That is, individuals who are unable to consent should be enrolled only when the research cannot be done as well with those who can give consent. Most would also agree that individuals who are unable to consent can be enrolled in research that poses minimal risk or in research where the benefit justifies the risk. Another safeguard, which is specified in federal regulations, is the designation of a surrogate decision-maker who can decide based on substituted judgment or the best interests of a participant. One study has shown that a reasonable proportion of individuals who can no longer consent for themselves retain the ability to assign a surrogate.[49] However, even surrogate decision-makers who know patients well might be unable to determine what decisions the patient might have made. Thus, another safeguard involves obtaining the patient's assent.[50]

There are no specific guidelines in the federal regulations with respect to these safeguards, beyond the designation of a legally authorized representative. However, the NIH Clinical Center has established a policy regarding the inclusion of adults who are unable to give consent. This policy emphasizes an educational component to provide reinforcement to help individuals understand. It also clearly defines

the responsibilities of principal investigators and institutional review boards, and it specifies that the Clinical Center will assess appointed surrogates.

Ethical Research Conduct for Potentially Cognitively Impaired in Chaotic Clinical Settings

Christopher Carpenter, MD, FACEP, AGSF
Washington University in St. Louis

Cognitively impaired patients tend to be excluded from studies because of their inability to consent, adhere to protocols, and provide longitudinal outcomes. Recently, an institutional review board (IRB) noted that this problem cuts across multiple specialties; that the status quo is equally unacceptable to patients, families, clinicians, researchers, and IRBs; and that IRB leaders are willing to share solutions.[51] The publications also included suggestions for real-world solutions to these challenges.[51] In this paper, the IRB suggested that, rather than exclude individuals with dementia, investigators should screen for decisional capacity and request an IRB-appointed proxy for those unable to consent. The IRB also suggested that intervention protocols and materials be adapted for the cognitively impaired and that corrective feedback and teachback be incorporated to ensure participants' understanding. In addition, the IRB suggested that investigators select alternative outcomes that have been adapted for the cognitively impaired. Measures to assess ADLs, quality of life, and pain among individuals with dementia have been developed and validated.[52-54]

Informed Consent for the Cognitively Impaired: Discussion

Dense and technical language is an overall challenge with consent forms. Memory aids are not meant to supplant consent forms, but investigators can work with IRBs to design aids that emphasize the most important information participants should know. Examples include recruitment brochures highlighting the risks and benefits of a study, assent documents as starting points for distilling important information from the consent, and pictorial synopses of consent documents. Such tools can be distributed to all participants, not just those who are cognitively impaired.

Another challenge in obtaining consent involves the "gray zone," where it is not clear whether an individual is able to give consent. In this zone, self-stigmatization is a concern; in some cases, patients may be offended when asked whether they understand the purpose of and risks associated with a study. Even so, assessing participants' capacity to make decisions and give consent is an ethical obligation. Failure to do so risks public trust.

Decisional capacity and clinical care is another concern. A Lancet publication in 2016 reported that, among individuals admitted to the hospital, about half lacked the capacity to consent to the treatments they received.[55] Researchers who identify participants with clinically significant cognitive impairment should alert families and clinical treatment teams about this impairment. How they do that will depend on the institution and must account for privacy issues.

Investigators also should keep the following in mind:

- Inability to consent is not a general category. Investigators should tailor safeguards to the type of study they are proposing.
- Staff who will obtain consent should be trained to conduct assessments of participants' capacity to give consent.
- Whereas there are almost no regulations regarding inability to consent to non-emergency research, regulations regarding emergency research in adults who cannot give consent are comprehensive and explicit.
- Advanced directives can include provisions for inability to consent. The advanced directive used by the NIH Clinical Center includes a section where individuals can appoint a research proxy and describe their preferences for research.

CUTTING-EDGE RESEARCH ON DELIRIUM AND DEMENTIA

Disentangling Delirium and Dementia

Sharon Inouye, MD, MPH
Harvard Medical School and
Hebrew Senior Life

The diagnostic criteria for delirium and dementia exclude each other and can be distinguished by onset, duration, attention, consciousness, speech, and psychomotor subtypes.[56] For example, delirium is typically abrupt and lasts hours to days, whereas dementia is insidious and progressive over months to years, and individuals with delirium are less able to sustain or shift their attention, whereas those with dementia exhibit normal attention unless their dementia is severe. However, there is an important interrelationship between delirium and dementia, and the two often coexist clinically.[57]

A systematic review of all prior studies across different populations found that the presence of dementia at baseline is a strong risk factor for the development of incident delirium, with a relative risk or odds ratio ranging from 1.3 to more than fourfold increased risk.[58] This same study found that delirium is a risk factor for subsequent dementia; one study in the review found a cognitive decline of six points per delirium day. Another systematic review showed an association between delirium and increased institutionalization and mortality.[57] Although addressed in only two studies in the systematic review, delirium emerged as a significant risk factor for subsequent dementia, with an odds ratio of 12.5. VANTAA 85+, a large, population-based study of more than 550 individuals aged 85 years and older, found a strong relationship between incident dementia and known pathologic markers such as tau, amyloid, vascular abnormalities, and Lewy bodies in persons without delirium.[59] However, this study found no detectable association between delirium and these markers, suggesting that the pathologic substrates for delirium might be distinct from those for dementia.[59] A study in mouse models at risk for dementia found an

association between inflammatory challenges such as lipopolysaccharide and neuronal death, microglial activation, and both acute and long-term cognitive deficits. Other studies found that microglial priming by Cox 1 and prostaglandin inhibitors can protect against these deficits.[58] Additional studies found that inhalational anesthetics can induce apoptosis, neurotoxicity, and changes consistent with AD.[58]

A link between delirium and long-term cognitive decline was observed in two clinical studies. One in 225 patients followed for 12 months after elective cardiac surgery showed an abrupt cognitive decline immediately after surgery.[60] Whereas individuals who did not experience delirium eventually recovered cognitively, those who had experienced delirium rebounded, but did not fully recover. Similar results were observed in the Successful Aging after Elective Surgery (SAGES) study, which followed patients for 36 months after major elective surgery.[61] Both those who did and did not experience delirium showed an abrupt cognitive decline and rebound, but those who had experienced delirium showed a significant decline below baseline at 36 months, following a slope equivalent to that seen in patients with known MCI. The risk for developing this decline was associated with delirium severity.[62] Likewise, another study of 771 individuals with AD found that those who developed delirium experienced a more rapid cognitive decline over 1 year, with a relative risk of 1.6 over those who had not developed delirium.

Who is at risk, the causes and mechanisms, and the relationships between vulnerability and precipitating factors for delirium leading to long-term cognitive decline, or complicated delirium, are not known. Thus, how to prevent and treat complicated delirium is not clear. Importantly, the prevention of delirium may offer the unprecedented opportunity to prevent or ameliorate future cognitive decline.

Assessment and Biomarkers Related to Dementia

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University of Wisconsin-Madison School of Medicine and Public Health

As demonstrated by the DIAN study, changes in cerebrospinal fluid (CSF) and imaging biomarkers precede the onset of AD symptoms by at least 20 years.[63] These changes were acknowledged in 2011 by the NIA/Alzheimer's Association diagnostic criteria, which included biomarker positivity for a diagnosis of probable AD with increased certainty.[64] As suggested by a recently published research framework,[65] the clinical diagnosis of AD will have to be confirmed through measures of amyloid and tau deposition and neurodegeneration. The paradigm-shifting framework will have to be confirmed through large, prospective clinical studies before it is adopted for AD diagnosis in clinical practice.

The diagnostic hallmark of AD is the extracellular amyloid plaque, which consists of an amyloid core surrounded by neuroinflammation, activated microglia, and dying neurons. Another hallmark is the intracellular neurofibrillary tangle, which comprises phosphorylated tau (p-tau). As axons die, tau is released into the CSF. Thus, CSF tau levels and Aβ deposition increase as CSF amyloid levels decline.[63] Accordingly,

abnormalities in diagnostic CSF and imaging biomarkers appear in order.[66]

Neuroimaging markers of AD include the appearance of marked atrophy in the hippocampus and parietal, temporal, and frontal lobes as seen by magnetic resonance imaging (MRI) and white matter and axonal disintegration and atrophy as seen by diffusion tensor imaging. Amyloid and tau deposition appear on positron emission tomography (PET), and reduced metabolism in the temporoparietal, posterior cingulate, and medial temporal lobe appear on fluorodeoxyglucose PET (FDG-PET). Other imaging markers include the appearance of neuroinflammation on PET and reduced activation with memory-encoding tasks in specific brain regions as visualized by functional MRI. It should be noted that AD-associated pathology appears in the brain long before symptoms do,[67] but the appearance of this pathology does not necessarily mean an individual will experience cognitive decline. The absence of amyloid deposition on PET scanning can rule out AD, but an individual might be resilient despite the presence of such deposition.

Several CSF biomarkers have been identified corresponding to amyloid deposition, neurodegeneration, neuronal and axonal damage and compromised white matter integrity. synaptic damage, and neuroinflammation. Of these, AB42, total tau, p-tau, and neurofilament light chain (NFL) have been shown to be the most robust and reliable in distinguishing AD from other dementias.[68] In a prospective Wisconsin cohort of 2,100 middle-aged, asymptomatic individuals with a parental history of AD, those positive for Aβ have shown the sharpest cognitive decline overall. As suggested by CSF and MRI data, multimodal biomarker assessment can distinguish four groups and provide some insight into what each group will experience with time.[69] For example, those with the classic AD biomarker profile (elevated p-tau and reduced CSF amyloid) show the fasted decline in cognitive function. Changes in CSF biomarkers also can reflect health behaviors such as sleep, physical activity, and diabetes control. Thus, future AD diagnoses will rely not only on biomarkers, but on multimodal assessments of these markers.

Assessment and Biomarkers Related to Delirium

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Beth Israel Deaconess Medical Center, Harvard Medical School

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) definition of delirium is difficult to apply at the bedside. Standardized assessments such as the Confusion Assessment Method (CAM) are easier to conduct in practice. CAM comprises four features: acute change and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. A diagnosis of delirium requires the presence of the first and second features, along with either of the third or fourth.[70]

Marcantonio and colleagues have developed a CAM-based diagnostic assessment that can be completed in 3 minutes (3D-CAM). Using a dataset of more than 4,500 CAM research assessments, the team has used item response theory to identify the most informative items for each feature.[71] In so doing, they have reduced

the pool from 120 to 36 items. Marcantonio and his colleagues have used multivariate modeling and logistic regression to further refine the item pool to 20 items. 3D-CAM has been validated in a prospective study of 201 general medical patients, 28% of whom had dementia.[72] Compared with the reference standard assessment, 3D-CAM identifies individuals with delirium, with a sensitivity of 90% and a specificity of 94%. When the study population was stratified by dementia, 3D-CAM showed 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. In response to feedback that even 3 minutes is too long, Marcantonio and colleagues collaborated with Fick to further refine the algorithm by identifying 3D-CAM items that can serve as brief screeners.[73] An algorithm in which this screener is followed by the full 3D-CAM is under evaluation in the READI study.

Marcantonio and colleagues also have conducted targeted biomarker discovery, using the SAGES cohort in a matched, nested case-control study. This study has identified two inflammatory cytokines, IL-2 and IL-6, that are significantly associated with delirium. IL-2 expression exhibits a pattern consistent with that of a risk marker, whereas IL-6 expression shows a pattern consistent with a disease marker. An untargeted proteomics approach also identified C-reactive protein as another inflammatory marker associated with delirium. These two studies therefore have demonstrated a strong association between delirium and inflammation, suggesting that delirium involves a heightened inflammatory response to stress and that there may be some inflammatory priming before surgery. A multiple-omics project on banked specimens is under way.

Postoperative Delirium and Cognitive Dysfunction—Searching for Clarity

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Duke Center for Cognitive Neuroscience and Duke Center for Aging

Postoperative cognitive dysfunction or decline (POCD) is defined as a postoperative decline in cognitive function as measured by cognitive tests both before and after surgery. Whereas delirium has specific diagnostic criteria, as outlined in the DSM-5, varying diagnostic criteria have been used across studies to define POCD. A recent publication has proposed a unified nomenclature for neurocognitive disorders, with more specific definitions for postoperative delirium, delayed neurocognitive recovery, and POCD based on DSM-5 criteria and the time of onset.[74]

Some have proposed that delirium and POCD reside on a spectrum,[75-77] because they share many risk factors, mechanisms, and sequelae.[78] A cohort study among patients having cardiac surgery has shown that those who showed initial cognitive deficits following surgery also showed a long-term decline over 5 years,[79] consistent with other studies showing a long-term decline despite an initial recovery after postoperative decline.[61]

Mechanistic studies in animal models suggest that anesthesia and surgery are associated with molecular processes associated with

AD.[80,81] Elevated CSF tau/ Aβ ratios have been associated with increased risk for delirium, and low CSF Aβ levels have been associated with increased risk for POCD.[82-84] However, whether anesthesia and surgery increases the risk for AD is controversial. The Markers of Alzheimer's Disease and NeuroCognitive Outcomes after Perioperative Care (MADCO-PC) study examined possible correlations between perioperative changes in tau and continuous changes in cognition among 110 patients aged 60 years and older undergoing major noncardiac, non-neurologic surgery. At 6 weeks after surgery, there were some changes in CSF-tau, but there was no significant correlation between postoperative tau changes and postoperative cognitive changes. However, changes in CSF tau levels from before surgery to 24 hours after surgery correlated with changes from before surgery to 6 weeks after surgery in the amplitude of low-frequency fluctuations (measured by fMRI scans) in the right supramarginal gyrus, a region that has previously been implicated in AD.[85] These findings suggest that a small postoperative change in CSF biomarkers may reflect longer-lasting focal postoperative changes in the brain. This hypothesis is under further study.

Cutting-Edge Research on Delirium and Dementia: Discussion

Delirium occurs in anywhere from 11% to 82% of individuals in institutional settings.[86] The highest rates are likely in the ICU and palliative care settings. The United States spends more than $16 billion per year on hospital costs associated with delirium and up to ten times that in health care and long-term care costs in the year following delirium episodes.[86] However, the causes of delirium remain poorly understood. Screening for and detection of delirium remain controversial, because there are no "magic bullets" as far as treatment. However, Big Data could help in identifying the true extent of delirium, and that requires documentation of delirium in the medical record.

More work is needed to understand the role of inflammation and neuroinflammation in delirium and dementia. Neuroinflammation plays a major role in dementia. Work in animal models has demonstrated inflammation as a key driver of long-term cognitive decline; however, cohort studies so far have not shown any correlation between acute inflammation and long-term cognitive decline. It is not clear why individuals experiencing postoperative delirium show long-term cognitive decline, even after they return to baseline in the short term. However, it may be that delirium sets up cycles of inflammation in the brain and that these cycles eventually promote cognitive decline. Other questions needing more study include the magnitude by which blood-brain barrier dysfunction in older adults is accelerated after surgery and whether disturbances in circadian rhythms mediate delirium and sundowning.

Multidisciplinary teams will continue to be important in answering these and other questions, but this will require the building of bridges across entrenched silos. Inouye and colleagues have responded to pushback on delirium research by training researchers in the field and by mentoring individuals from other disciplines before they become too siloed.

RESOURCES FOR JUNIOR INVESTIGATORS

Cognitive Impairment in Research: Introduction to the NIH TOOLBOX®

Molly Wagster, PhD
National Institute on Aging

The NIH TOOLBOX® for Assessment of Behavioral and Neurological Function arose from a blue-ribbon panel convened in 2004 by NIA, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke. This panel found it difficult to draw conclusions about risk and protective factors in cognitive, emotional, and behavioral health because of the lack of standards and uniformity in measures. This lack of standards also hinders the ability of investigators to share and integrate research results. NIH therefore set out to design a set of measures to assess a range of brain health and function, not just diseases, and to assess change over time. NIH emphasized innovative and cutting-edge measures; existing measures would be included where possible, and new measures would be developed when needed. In addition, the NIH required the measures to be dynamic and therefore adaptable over time in response to changing technologies.

The NIH TOOLBOX (www.nihtoolbox.com; see also http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox/intro-to-nih-toolbox for an introduction to the measures and http://www.healthmeasures.net/images/nihtoolbox/NIH_Toolbox_brochure_June_2017.pdf for a handy summary) is a multidimensional set of brief, well-validated, psychometrically sound measures to assess cognitive, sensory, motor, and emotional functions across diverse study designs and settings. Each domain battery is designed to be administered in 30 minutes or less, and domain-level batteries are available in English and Spanish. Individual measures are nationally normed for ages 3 to 85 years. They are now available for use on the iPad. The NIH TOOLBOX and other NIH-supported measurement systems, such as the Patient-Reported Outcomes Measurement Information System (PROMIS), are available at www.healthmeasures.net. Validation of the NIH TOOLBOX measures are under way in specific patient populations. For example, this past year, Northwestern University was awarded a grant by NIA to validate NIH TOOLBOX measures in persons with amnestic MCI and early AD and to extend the validation of the measures beyond the age of 85 years.

NIH continues to emphasize, encourage, and facilitate data-sharing, and it is engaging in efforts to support Big Data and the development of common data elements. NIH also supports initiatives, such as the Precision Medicine Initiative, now known as All of Us, which aims to provide individualized diagnosis and care for patients. Major efforts such as these will benefit from the use of common measures across studies, a need that well-validated, easy-to-use assessments such as those found in the NIH TOOLBOX can help fill. It should be noted that NIH does not aim to hinder creativity or the development of new measures nor suggest that the NIH TOOLBOX measures should be used

exclusively in future studies. NIH encourages the use of NIH TOOLBOX measures in all relevant clinical research as the primary measures or in addition to the primary measures, in order to facilitate data-sharing and comparison of findings across studies and in clinical settings.

Inclusion of Racial and Ethnic Minorities in Cognitive Research

Raj C. Shah, MD
Rush University Medical Center

According to the National Vital Statistics Report, the lifespan of individuals almost doubled during the 20th century, from 46 to more than 80 years. This has resulted in a large increase, both in the United States and worldwide, in the absolute number of individuals older than 65 years. There has been some improvement in racial/ethnic gaps in life expectancy, from a 13-year gap between white and black individuals in 1900 to a 3-year gap in the present. Yet, full equity has not been reached. In addition, the U.S. population is becoming more diverse, and about 45% of individuals older than 65 years are nonwhite. Broader public health initiatives, such as Healthy People 2020, are working to reduce racial and ethnic health disparities. Thus, investigators should ensure that the research results they obtain apply to a wide range of individuals older than 65 and the experiences they have.

Frameworks have been developed in this regard. The broadest, developed by the Centers for Disease Control and Prevention, is the Health Impact Pyramid. This pyramid moves from socioeconomic factors such as poverty, housing, and education, which have the largest impact and broadest level of influence, to clinical interventions, counseling, and education, which focus more on the individual but have a smaller impact. The NIA Health Disparities Research Framework (Figure 4) presents fundamental factors and levels of analyses to consider when including diverse populations in research. Adler and colleagues have also proposed mechanisms to explain how sociocultural factors influence behavior and biology.[87,88] Thus, investigators have the opportunity to build models for how environmental, sociocultural, behavioral, and biological factors interact.

The NGAGE model,[89] which has been developed over 15 years, provides a systematic way to think about engaging diverse populations in research. The model emphasizes 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. Investigators should keep certain pitfalls in mind. Not only should they be curious about diverse life experiences, be mindful of important scientific questions that require diversity, and appreciate the history of prior engagement in diverse communities. They also should consider switching "control" groups occasionally, offering team membership to individuals from the community, engaging again after the first attempt, enabling community engagement in research design decisions and information dissemination, and establishing systems in advance to measure important engagement outcomes. Long-term engagement should also be considered.

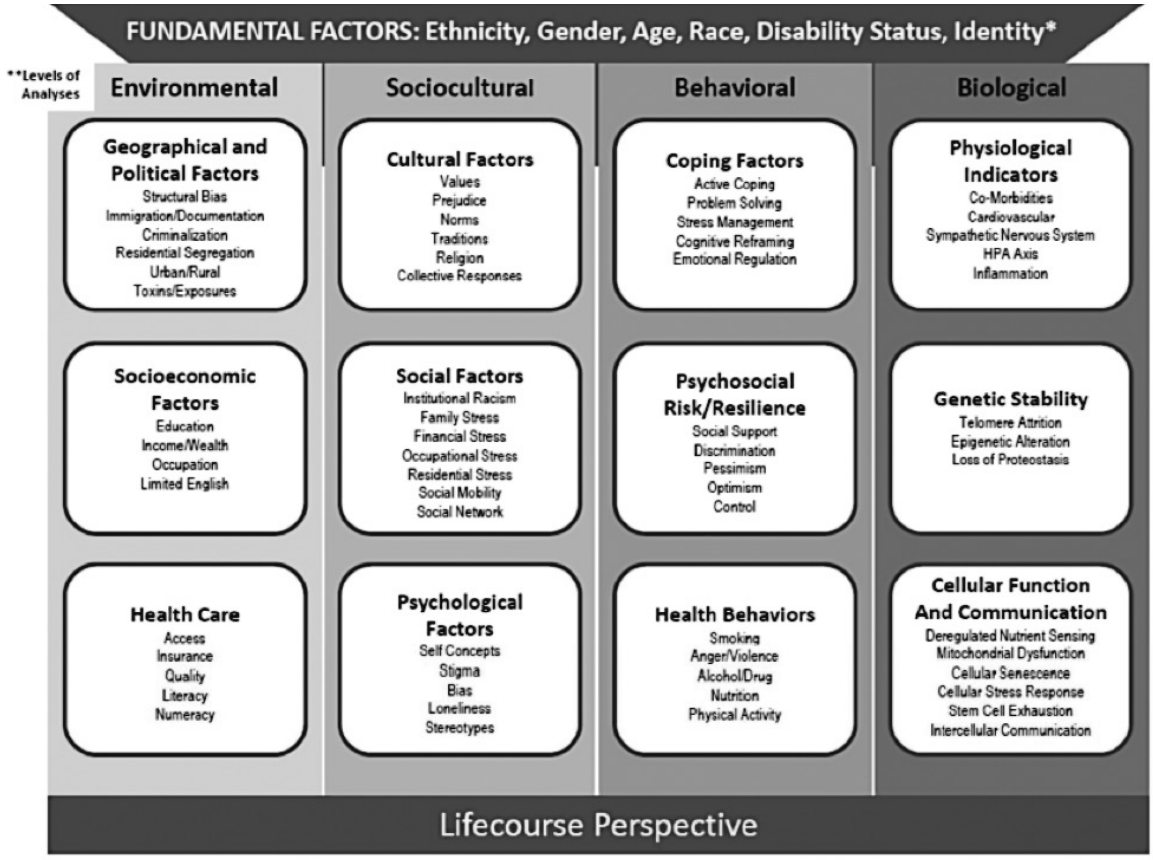

Figure 4. NIH Health Disparities Research Framework. *Sexual and gender minorities; **Text within boxes represents examples of related factors. (Shah presentation slide 12)

Use of Databases and Big Data in Cognitive Research

Dan Mungas, PhD
University of California, Davis

Data resources include proprietary data such as web behavior data, publicly accessible databases such as health claims data, electronic health records (EHRs), and shared research data collected around specific questions. The two main dimensions of structure are the size of the resource and whether it is designed for research. Large databases designed to answer a specific research question are rare, if they exist at all. EHR and publicly accessible administrative databases may or may not be designed to answer specific questions, whereas web behavior data sources usually are not. With respect to questions around cognition, smaller databases generated from individual or collaborative studies tend to offer more comprehensive and focused data, whereas larger databases, such as those focused on web behavior, tend to offer limited data on cognition. EHR and administrative databases can include clinical diagnoses or screening measures, while epidemiologic databases include clinical diagnoses and more comprehensive cognition measures.

A recent white paper[90] described a large, international survey in which respondents overwhelmingly agreed on the need for data-sharing and were willing to share their data. However, data-sharing is hampered by issues such as some investigators' willingness to share and recipients' difficulties in identifying and accessing shared data. Both investigators and recipients have difficulties in managing data-use agreements, which are necessary to protect study participants' confidentiality, assure compliance with the Health Insurance Portability and Accountability Act, promote the responsible use of data, and allow principal investigators some level of control over the data they have collected. These agreements increasingly involve contracts between the investigator and recipient's institutions. However, there is no uniformity among these processes.

NIH-funded studies, including those focused on cognitive aging, are required to share data. In addition, NIA has funded the Advanced Psychometric Methods in Cognitive Aging Research Conference since 2008. Examples of public datasets and those used in the psychometrics conferences are listed below (Table 1):

Table 1. Examples of Datasets for Dementia Researchers

Public Datasets	Datasets Used in Psychometrics Conferences
Health and Retirement Study (https://hrs.isr.umich.edu/data-products)	**Rush Religious Orders Study (ROS) and Memory and Aging Project (MAP)**
National AD Coordinating Center (https://www.alz.washington.edu)	**Washington Heights Inwood Columbia Aging Project**
AD Neuroimaging Initiative (ADNI) http://adni.loni.usc.edu/data-samples/access-data/	**UC-Davis Diversity Cohort**
	Reasons for Geographical and Race Disparities in Stroke (REGARDS)
	Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE)
	Framingham Heart Study
	Adult Changes in Thought (ACT)
	Integrative Analysis of Longitudinal Studies on Aging (IALSA)

Recipients can identify relevant datasets by searching the research literature or by contacting primary authors, local investigators working in a target area, or principal investigators on grants. Scientific questions for analyses must be matched to the dataset characteristics. It is possible to merge data from different datasets through meta-analysis, replication, or harmonization, but these approaches require increasing levels of similarity in variables across studies.

In the era of Big Data, many repositories have high-dimensional data collected under rigorous protocols, and data-mining and machine-learning technologies are used to explore possible associations. At this point, however, data on cognition are limited. Again, the research question must be tailored to the amount, type, and quality of available data. Administrative help should be available to facilitate access, and programming expertise should be available to aid in managing the data and extracting relevant variables.

Resources for Junior Investigators: Discussion

The measures in the NIH Toolbox are designed to adapt to new technologies without losing the ability to track performance over time. However, there are no funds set aside specifically to update these measures. It should be noted that the NIH Toolbox is not designed to be a comprehensive, state-of-the-art measurement in each individual domain. Rather, it is designed to provide investigators from all disciplines with a ready-made set of valid, psychometrically strong, normed measures to be used as an adjunct to their studies. Investigators are encouraged to add these measures to provide some uniformity across studies.

Engaging with and including diverse populations in studies is an iterative process that investigators should monitor constantly to allow for mid-course correction. If investigators are not recruiting the population they want, they should assess whether they are introducing unknown barriers, as well as dynamics or variables affecting how prospective participants make decisions regarding participation in a study.

IRB-approved consent forms present one barrier to data-sharing. For example, investigators on the SAGES study want to share data, but the IRB-approved informed consent does not permit them to share de-identified data. They are also prevented from data-sharing by the time and expense required to create a minimum dataset. Although NIH can require data-sharing as a condition for award, it cannot interfere with local IRBs. Investigators should work with their IRBs and contracting officers early on to facilitate data-sharing. The Center for Open Science might also provide advice in this regard.

NIA RESEARCH DIRECTIONS

Robin Barr, DPhil
National Institute on Aging

The 2018 Appropriations Act continues the Federal government's commitment to funding research on AD and increases funding for AD research by $414 million. That money goes to the NIA budget, bringing the Institute's total budget to more than $2 billion. NIA also is receiving a portion of the $500 million given to

NIH over 2 years to address opioid addiction. NIA has 100 active FOAs, 70 of those focused on AD. Only 37 FOAs support R01 research; other mechanisms include P01 and U19 program projects and R25s to teach undergraduates about science in aging. Fourteen of these FOAs are earmarked for small business research to aid in disseminating health advances to the community.

NIH also expects to continue its focus on emerging investigators and first-time renewals for young investigators, with actions to significantly reduce the average age of NIH-supported investigators. In scoring applications, NIA gives a five-point advantage to R01 applications from early-stage investigators and a three-point advantage for those from new investigators. This helps NIA to meet its requirement for increasing the number of awards it makes to early-stage investigators. Most awards to early-stage investigators come from GEMSSTAR, the Beeson program, other career development award programs such as the K23 mechanism, and pilot grants. The Center for Scientific Review also offers the Early Career Reviewer Award Program, which encourages young or early-stage investigators to serve on study sections as third reviewers.

Discussion Points

- Unlike funds provided to NIH by the American Recovery and Reinvestment Act, the funds from the 2018 Appropriations Act are targeted specifically to AD research. This does not affect the Beeson Award, which has a separate allocation.
- The National Cancer Institute is starting a program that awards early-stage investigators their first R01 for 5 years, with an option to renew for 2 years without a competing renewal. This program is not possible for NIA.
- Although R21s can provide some experience for early-stage investigators, they are not stepping stones to R01s. R21s are explicitly designed to support the design of tools or models for research.
- Academia is increasingly recognizing the contributions of team science, and some universities are starting to change their promotion paradigms accordingly.

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Conflicts of Interest

1. SA received grants from NIA/NIH to conduct Alzheimer's disease research. SA received grants from Merck Pharmaceutical, Eisai, Toyama Chemical and Lundbeck to serve as a Site PI for clinical trials involving patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Please note these grants were awarded to UW-Madison. SA received royalties from McGraw Hill Education as an Associate Editor for the textbook entitled "Hazzard's Geriatric Medicine and Gerontology."

2. MB receives grant funding from NIA K76 AG057022 and NIA R03 AG050918, additional funding support from NIA AG028716, and funding from the Alzheimer's Drug Discovery Foundation. MB serves as a board member for Early Stage Anesthesiology Scholars (eSAS), and liaison from the American Society of Anesthesiology to the American Geriatrics Society.

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

4. AH receives research funding from GSK, Celgene, and Novartis. AH served as a consultant for: MJH Healthcare Holdings, LLC, Pierian Biosciences, Boehringer Ingelheim Pharmaceuticals and Sanofi. AH serves as Board Member for ASCO.

5. 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.].

6. JV received grant funding from NIH. JV participated in a consultancy for Saint Care Corporation, Japan.

Author Contributions

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

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Dedication

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

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