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Military risk factors for Alzheimer's dementia and neurodegenerative disease☆

The linkage between head trauma and neurodegeneration represents not only an important public and military health issue but also provides crucial clues for putative risk factors for numerous late-life chronic brain disorders. Today, there is now growing evidence that a single traumatic brain injury (TBI) sustained early in life might trigger a cascade of neurodegenerative processes. The outcomes may manifest as dementia, Alzheimer's dementia (AD), Lewy Body dementia (LBD), or other motor neuron diseases many years or decades later. The scientific and medical community has known the effects of trauma on boxers since the 1920s.

Now, increasing number of studies are showing that even mild repetitive trauma may lead to onset of symptoms in some athletes as early as in their second decade of life. The renewed interest in the idea that mild repetitive trauma to the head can trigger not only chronic traumatic encephalopathy (CTE) but also other neurodegenerative diseases is indeed timely. This important recognition is reinforced by the increased risk and prevalence of TBI and post-traumatic stress disorder (PTSD) among young military personnel associated with combat experiences.

Understanding the neurobiological mechanisms of the association of TBI and PTSD with an increased risk of neurodegenerative disease has become a high priority for the U.S. Army. Civilian public health research shares this military health interest and highlights a common critical challenge: *the development of novel technologies for the early and accurate identification of people with elevated risk for neurodegenerative diseases.*

An early challenge for military and civilian health research will be to unlock complex, intersecting associations and interactions among multiple risk factors (such as proteins, genes, and environment factors). This work will require more robust and granular longitudinal data, the collection of data parameters that may vary daily or hourly, and the application advanced data analytics and mathematical modeling. This intensive exploration should spur development of critical detection technologies. These tools will enable individuals with elevated risk to make informed lifestyle choices that limit head trauma *exposures*. Moreover, the answers found in studies of trauma-induced neurodegeneration are likely to increase our understanding of the entire spectrum of neurodegenerative diseases as well as other age-associated chronic brain disorders [CBD].

Neurodegenerative diseases [ND], as a prototype for other CBD, represent an important class of conditions for healthcare systems due to their prolonged labor-intensive care requirements and profound economic impact. These conditions have severe psychosocial ramifications that may span an entire human lifetime. Moreover, ND are emblematic for a host of other long-lasting incapacitating conditions that require a global response.

Leaders in governments, businesses and academia recognize the need for a well-coordinated strategic international plan. Moving forward, planning efforts should establish financial mandates for strengthening the worldwide scientific capabilities, infrastructure, and resources for research and development. Such investments will have the net-effect on reducing the *duration* of chronic brain disorders and/or the *number of people* at risk for these conditions. Budget outlays should be coupled with sound legislative and policy initiatives to foster broader engagement through public–private partnerships. History has proven that collaboration among academic investigators, government, pharmaceutical, and biotechnology companies is an essential ingredient in advancing bold initiatives, particularly when resources are limited.

International plans to combat Alzheimer's dementia, TBI and other CBD must address the pressing need to accelerate breakthroughs for ever-earlier detection of individuals at risk as well as a wide spectrum of intervention to limit the progression of neurodegeneration before the onset of disabilities or symptoms. The societal burden of these disorders—spanning early-, middle- and late-life—merits harmonized international planning efforts that should encompass three related aims. The first is the development of shared international research infrastructure resources (IR2s). The second is related organizational management

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structures to administer and operate these new shared resources. The third is expansion of global investigator networks that will optimally develop, exchange and disseminate new knowledge. Building upon already existing programs and initiatives, including those developed and funded by the U.S. Department of Defense, Veterans Administration and the Department of Health and Human Services, and by leveraging other existing international resources offers the fastest pathway to meet these goals.

The discovery of risk factors, biomarkers, and surrogate indices for neurodegeneration will be enhanced through the development of a shared *international research infrastructure resource* (IR2). One research application is the combinatorial optimization and validation of disease specific *risk factors-biomarkers-surrogate indices matrices.* This challenge requires longitudinal, large-scale ($n > 100{,}000$) international prospective clinical and observational data in order to have sufficient power and resolution for modeling and hypothesis testing. Developing a sufficiently large data reservoir to support specific (and varied) research questions is essential for the rapid translation and regulatory approval into useful, routine, clinical tools for accurate prognosis and diagnostics of individuals. In this example, to assure validation and regulatory market approval, a key requirement for the research project using a shared IR2 will be the availability of large and diverse cohorts—spanning the lifespan—of heterogeneous populations. This will include healthy young-, middle- and late-age adults as well as individuals at elevated risk of developing neurodegenerative disease.

Conceptualizing and launching the organizational structure, administration and functional capabilities of this IR2 will depend on the recruitment of large numbers of volunteers to meet the data needs of multiple projects exploring multiple hypotheses among diverse populations. The shared IR2 will provide the world scientific community an unprecedented opportunity to plan and execute a wide range of population-based and naturalistic studies to solve critical questions related to public health, aging and individual brain disorders. The shared IR2 will have the capacity to support various activities such as the discovery and validation of biomarkers, epidemiological studies to assess potential risk factors, and aid in the identification of individuals' occupational specialties that reduce the likelihood of head injuries.

The multi-factorial nature of CBDs will also require sophisticated *computational capabilities* for pattern analysis of various indicators, as has been the case in genomics and proteomics studies. The goal will be to identify relevant sets of indices so that when an intervention becomes available, appropriate individuals can be selected to test its effectiveness. As instruments and biomarker progress to measure neurodegeneration in the earliest stages of onset, questions about the fundamental mechanisms that underlie CBD can be more fully explored. This includes: *a) understanding why some neurons are, and others are not affected, b)* the precise nature or cause of the failure-disruption in the functioning of some specific neural systems, *while other networks remain intact*. Answers to these questions are pivotal to the development effective preventive interventions.

So where to start? The next steps should focus on expanding ongoing collaborative effort and build upon the experiences gained from already-established, ongoing international collaborative efforts, such as the Worldwide Alzheimer Disease Neuroimaging Initiative (ADNI), the U.S. Department of Defense-ADNI, the Alzheimer's Association Global Biomarker Standardization Consortium and the Global Alzheimer's Association Interactive Network.

The transition of these and other shared IR2s into large international enterprises will require new models of governance and financing to sustain multi-decade long operation. The Alzheimer's Association in partnership with Campaign to Prevent Alzheimer's by 2020 has taken the leadership in launching one formal strategic planning process by convening a workgroup on *Big Data to Smart Data*. Future international planning efforts should remain focused on integrating solutions from the worldwide collaborative research enterprise, with a special emphasis on new models for research finance. This convergence of efforts will speed development of interventions to meet the urgent needs of public and military health in combating Alzheimer's dementia and other neurodegenerative diseases.

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