Behavioral and Social Research in the Geroscience Agenda: Translation, Health Disparities, Trial Design, Outcome Measures, and Novel Prevention Targets

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Abstract: Geroscience is the study of how to slow aging, aiming to extend health span. Geroscience has not heretofore incorporated behavioral or social-science research into its agenda, but the current expansion of the agenda to human trials of anti-aging therapies will be greatly aided by behavioral and social-science research. This article recommends some ways in which geroscience can be augmented through behavioral and social science research aiming to: accomplish translation from animal models to humans; reduce and not exacerbate health disparities; inform the design of clinical trials of anti-aging therapies; develop outcome measures for evaluating efficacy of anti-aging therapies; and identify novel anti-aging prevention targets, in particular mental health.

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Introduction.

Geroscience is the study of how to slow aging, aiming to extend health span. It has not heretofore incorporated behavioral or social-science research in its agenda, because geroscience researchers have been intensely focused on studying mechanisms of aging at the molecular and physiological level, primarily in non-human model organisms in the laboratory. However, the geroscience agenda is currently expanding to initiate human trials of anti-aging therapies, and this expansion will be greatly aided by behavioral and social-science research. This article recommends some ways in which the geroscience agenda can be augmented through behavioral and social science research.

The geroscience hypothesis.

The geroscience hypothesis proposes that aging is the underlying cause shared by all age-related diseases, and therefore therapies that are able to slow aging should also be able to reduce all diseases and extend human health span, i.e., years of life lived without disability (https://nia.nih.gov/research/dab/geroscience-intersection-basic-aging-biology-chronic-disease-and-health). In geroscience, aging is controlled by molecular and physiological fundamental processes, such as macromolecular damage, metabolism, proteostasis, cellular senescence, chronic inflammation, epigenetic factors, and stem-cell regeneration, all of which are very closely interrelated within the organism. Animal-model geroscience research delving into these fundamental aging processes has shown that it is possible to slow these processes of biological aging

through administering genetic, nutritional, and pharmacological treatments. The intoxicating promise of the geroscience hypothesis is that it is possible to develop therapies that are capable of slowing human aging. According to the geroscience hypothesis, a therapy that can slow biological aging will inherently slow the onset and progression of a host of age-related cardiovascular, sensory, neurodegenerative, immune, and musculoskeletal diseases, simultaneously (Barzilai et al., JAMA, 2018). The geroscience approach aims to find a prevention silver bullet. A treatment that will be able to prevent many diseases at once, and before they onset, has attractive potential benefits over the current approach, which is treating each disease one at a time after diagnosis, in an attempt to reverse organ damage. The success of this agenda would have wide-ranging implications for not only medicine as traditionally practiced, but also for economics, social structure, human wellbeing, and bioethics (Nuffield Council on Bioethics, The search for a treatment for aging, 2017).

How might behavioral and social research augment this exciting geroscience agenda? Sections below will suggest that behavioral and social-science research is necessary: (a) to accomplish translation of geroscience findings from preclinical animal models to human population health, (b) to study how the geroscience agenda can reduce and not exacerbate health disparities, (c) to inform the design and implementation of strong clinical trials of anti-aging therapies, (d) to develop outcome measures for evaluating the success of anti-aging therapies, and (e) to identify novel anti-aging prevention targets, in particular mental health.

Translation of geroscience: The leap from lab to life will be supported by behavioral and social research.

Therapies to extend health span are poised to make the move from laboratory animal models to human clinical trials (Tchkonia and Kirkland, JAMA, 2018). Translation from mouse to human will entail challenges, among them the multifactorial heterogeneity of human aging. The move from slowing fundamental processes of aging in laboratory animals to slowing aging in humans will not be as simple as prescribing a pill and watching it work. Aging in laboratory non-human animals under controlled circumstances is not only different from aging in humans, it is different from aging in free-ranging non-human animals who live under natural conditions. In recognition of this gap, geroscientists are studying domestic pet dogs (http://dogagingproject.com/). However, compared to aging in laboratory animals and free-living domestic animals, human aging has even more heterogeneous multifactorial origins and influences. These influences include potential intervention targets that are uniquely human, and therefore are not easily investigated in animal research. Oft-studied examples might include: personality traits, intelligence, loneliness and social connection, purpose in life, stressful early-life adverse experiences, or psychiatric history (which predicts short healthspan). Humans vary widely on such factors, and this variation generates differences between individuals in the pace at which they age. Individual differences in the pace of aging, like causal heterogeneity of aging, will complicate translation.

A human adult's pace of biological aging may be sped or slowed by familial genetic endowment, by varying early-life experiences and exposures, and by individual differences in a number of lifestyle factors, such as diet, physical activity, sleep, and

smoking. One study reported that individual differences in the pace of biological aging among adults tracked from age 26 to 38 was independently predicted by personal-history characteristics present in their childhood: adverse experiences, social-class, health, intelligence, and self-control, all measured in childhood, predicted differences between individuals in their pace of aging, over and above prediction from grandparents' longevity. Participants who accumulated more of these personal-history risks showed a faster pace of biological aging over the dozen years of the study (Belsky et al., Aging Cell, 2017). Human-relevant factors like these have not been studied in geroscience's animal models. However, there is an awful lot of human observational research that shows early-life risk factors can statistically predict hard aging endpoint outcomes such as the timing of late-life disease onset, as well as early mortality. To assist geroscience translation, behavioral and social-science research needs to push harder to test whether these predictive associations are, in fact, causal. Behavioral and social scientists can apply research designs, such as whether twins who are discordant for behavioral/social risks age at different rates, whether biological age speeds up from before to after participants' risk-exposure in longitudinal studies that use the self as one's own control, and whether biological aging slows in response to behavioral/social intervention trials. Behavioral and social factors that causally influence the pace of aging must be researched and understood because they will inevitably complicate translation of geroscience findings from preclinical animal models to human anti-aging therapeutics.

It has been remarked that people don't age in labs, they age in life. There is a need to get geroscience out of the laboratory and into the world, where people age.

Moving from preclinical models to anti-aging interventions with humans will work better to improve public health if there is an intermediate step of testing the tenets of geroscience against the tenets of human epidemiology. Population-level studies of geroscience findings are needed to reveal the effect sizes of geroscience variables in the context of human population aging. Are effect sizes large enough to meaningfully affect population health? Geroscience findings should be put to standard tests such as attributable risk, sensitivity, specificity, number-needed-to treat, and positive and negative predictive values. Behavioral and social scientists are expert in epidemiological research in the context of large cohort studies, and can undertake this work.

Geroscience and health disparities.

Health disparities is the term used to explain that health span, quality of life in later years, and mortality tend to vary by socio-economic status, urban-rural residence, race and ethnicity, sex, gender, and sexual orientation. Disadvantaged groups need anti-aging therapeutics most. Yet, it cannot escape notice that those invested in the geroscience agenda so far tend to be from advantaged groups. The geroscience agenda needs to be integrated with the health disparities agenda. To demonstrate the benefit of potential anti-aging treatments for improving the health of the population, clinical trials of geroscience-derived treatments will need to recruit individuals with personal histories of socio-economic disadvantage, low educational attainment, adverse early-life experiences, and other sources of health inequality, because these are the people who age fastest and die youngest. Trials evaluating anti-aging therapies must effectively represent populations who are most in need of these therapies. Behavioral and social science tools can be applied to improve understanding of basic biological

processes of aging in health disparity groups, and to augment recruitment of health-disparity groups into clinical trials.

Clinical trials of geroscience-derived anti-aging therapies will be informed by behavioral and social research.

Consider the difference between imposing caloric restriction on caged laboratory mice to slow their aging, versus imploring free-living middle-aged humans to restrict calories and maintain weight loss long-term, even with the attractive carrot that caloric restriction should extend their health span. Even if there were an anti-aging pill, which would be easier to take than a caloric-restriction program, patients commonly fail to follow prescription-medication regimens properly, and sustaining adherence is a major barrier in pragmatic trials. Non-adherence is known to be predicted by patients' behavioral and social characteristics. Furthermore, the same behavioral and social personal-history characteristics that predict rapid pace of aging have also been shown to influence who volunteers for trials, who adheres to treatment regimens, and who completes treatment protocols. These adherence-relevant personal-history characteristics include low conscientiousness and cognitive dysfunctions, among others. By the end of a randomized trial, this state of affairs may reintroduce the bias and confounding that random assignment to trial arms was intended to eliminate (Demets and Cook, JAMA, 2019). For this reason, the marked heterogeneity in causal influences on humans' aging will probably complicate and even compromise clinical trials of anti-aging therapies.

Humans' behavioral and social personal-histories may also influence their response to treatments. For example, individuals who grew up with a socially

advantaged behavioral and social background could already be aging slowly, and such slow-agers might be unlikely to show benefit from treatment. Individuals who grew up with a socially disadvantaged behavioral and social background could be faster-agers, who might be able to show more benefit from treatment. Randomized clinical trials are obliged to register in advance participant characteristics that will be analyzed as potential moderators of treatment outcome. Information about behavioral and social personal-history characteristics that influence the pace of human aging could potentially improve trial design and pre-registration, by pointing to potential moderator variables. If we knew more about factors affecting the pace of human aging, trials could be planned in ways that maximize chances of success. Overall, to enhance the translation of novel antiaging intervention strategies for humans it will be necessary to know what factors, including behavioral and social factors, create individual variation in the pace of aging in not only older adults, but in young-to-midlife adults too. This is because the young-to-mildlife demographic group is the eventual market for anti-aging therapies aiming to prevent disease onset.

Finally, behavioral and social research will need to inform implementation science that is needed in order to span the gap between having a promising anti-aging treatment and having it actually work to improve the health of the population. Even the most effective of treatments often stumbles at implementation. How to get doctors to prescribe it? How to get patients to adhere to regimens? What happens if unequal access to a treatment exacerbates health inequalities? What if antiaging therapies don't work for everyone? These are potentially behavioral and social questions.

Behavioral and social research can develop outcome measures to evaluate geroscience-derived therapies.

Scientists have been able to quantify and manipulate the pace of aging in non-human model organisms in the laboratory, and announcements have been made that promising anti-aging therapies are ready for human trials (Longo et al., Aging Cell, 2015; Tchkonia and Kirkland, JAMA, 2018). But an obstacle blocks the translational pipeline: a lack of technology to measure the pace of aging in young humans. Why young humans? Anti-aging therapies administered to young people have the best chance of accomplishing geroscience's goal of preventing or delaying the onset of age-related diseases and thereby extending healthy years of life (Moffitt et al., J of Gerontology A, 2017). Young adults' organ systems are not yet damaged by disease; for them anti-aging therapies need only to slow aging, not reverse it. However, a technical problem arises because if an anti-aging therapy is administered to individuals in their forties instead of their seventies, a clinical trial will have to last over 30 years in order to detect the therapy's effects on endpoint outcome measures of disease-onset, frailty, and mortality. That lengthy duration is obviously undesirable. To make progress, mid-life intervention trials must have outcome measures that are sensitive to biological aging in young people, long before disease onset (Niedernhofer, Kirkland, & Ladiges, Aging Research Reviews, 2017).

Work to develop such measures is well underway. For example, in neuroscience, recent research has derived measures of brain age by training research participants' whole-brain structural neuroimaging data to the criterion of their chronological age. A brain-age measure is appealing because it requires only a single brain MRI test (Cole

and Franke, Trends in Neurosciences, 2017; Cole et al., Molecular Psychiatry, 2018). As another example, epigenetic “clocks” have been created by training research participants’ methylation profiles on their chronological age, on the assumption that older chronological age mirrors more advanced biological age. An epigenetic clock is appealing because methylation measurement in peripheral tissue requires only a single blood test (Horvath, Nature Reviews Genetics, 2018). However, there are many questions about the usefulness of the clocks as a measure of biological aging for trials of anti-aging therapeutics, and these questions need to be evaluated (Belsky et al., Am J of Epidemiology, 2017; Zhang et al., BiorXiv, 2018). A long-established rule of thumb in the science of human development is that findings from cross-sectional comparisons between groups of different-aged individuals do not guarantee findings about measured longitudinal change within the same individual over time (Schaie, The Geronotologist, 1967). This rule of thumb implies that the assumption that methylation in participants of older chronological age represents their advanced biological age may not be wholly correct; compared to younger participants older participants also had elevated exposure to childhood diseases, tobacco smoke, airborne lead, and less exposure to antibiotics and other medications, lower quality nutrition, and less education, each of which may alter the methylome. More studies are needed of age-related decline in multi-wave repeated measures of biomarkers within the same individuals, and these will emerge from longitudinal cohort studies. A multi-biomarker panel of aging-sensitive measures has been tracked with repeated measures at age 26, 32, 38 and 45 years in one population-representative cohort, yielding an index of each participants’ pace of aging that represents the pace of change within an individual over time. This pace-of-aging

index was found to be linked to cognitive decline, lower functional status, and accelerated facial aging in midlife (Belsky et al., PNAS, 2015), as well as to cortical thinning of the cortex (Elliott, et al. in review). Further, in a randomized controlled trial, caloric restriction disrupted a multi-biomarker measure of biological aging (Belsky et al., J of Gerontology A, 2017). There is initial proof of principle for deriving an epigenetic DNA methylation signature that captures decades of biomarker decline in a single blood test (Author, forthcoming, personal communication).

Methods to measure the pace of aging in humans who have not yet developed chronic disease would make it possible to record and quantify pre-treatment baseline, during-treatment change, and post-treatment outcome in turn, for participants in randomized clinical trials of anti-aging therapies. A good pace-of-aging measure needs to be a strong predictor of late-life disease and mortality, but it also needs to be feasible for use with young-to-midlife adult trial participants, for whom disease and death are far in the future. Practical, repeatable, inexpensive measures of how fast a young clinical-trial participant is aging are needed to show which treatments work, and which do not, and for whom. On the one hand, participants who are already aging slowly may have little room to improve in a therapeutic trial. On the other hand, those who are aging most rapidly might be treatment-resistant. Measures must be developed to allow research into these possibilities.

To date, the race to develop outcome measures for geroscience clinical trials of anti-aging therapeutics has not included measures of cognitive or social aging. Improved health span will not be merely a matter of the absence of disease; enhanced population health must include more years of sustained intellectual vigor, social

participation, physical function, and wellbeing. It should not be assumed that because biomarkers improve, social and behavioral outcomes will naturally follow. In fact, not much is known about how measured biological aging relates to measured social and behavioral aging. (Many of us know an older adult whose cognitive and social functioning are notably impaired, while their bodily health remains relatively robust.) Behavioral and social scientists should act to insure that not only biomarkers, but behavioral, cognitive, functional, and social outcome measures are included as outcomes in clinical trials of anti-aging therapeutics.

Mental health could be studied as a potential geroscience prevention target.

Mental disorders are often overlooked when aging researchers speak of chronic conditions that are related to an individual's pace of biological aging. Yet, mental health may be an excellent target for slowing aging and preventing late-life age-related diseases (Moffitt and Caspi, JAMA-Psychiatry, 2019). Behavioral and social scientists offer expertise in researching mental health. There is some empirical evidence that mental disorders accelerate biological aging, and importantly, they are treatable. The peak age for onset of mental disorders is the first 3 decades of life, which makes them temporally antecedent to the peak age for onset of age-related diseases, thus ideally timed to be causal in the aging process. Studies of both cohort datasets and official medical-record datasets have shown that individuals who experienced mental disorders in early life also tend to experience age-related diseases and early mortality in late life, at elevated rates that markedly exceed statistical chance (Lawrence et al. BMJ, 2013; Scott et al., JAMA-Psychiatry, 2016). Mental disorders are not rare; they affect a considerable portion of the population. Depression alone is perennially at the top on the

Global Burden of Disease list. Moreover, for a substantial percentage of individuals who experience an episode of mental illness in early life, the disorder becomes a chronic condition persisting for many years into late life. This applies to major depression, anxiety disorders, psychotic illnesses such as mania and schizophrenia, and to drug and alcohol addiction.

Mental disorders are known to be characterized by processes that should accelerate biological aging, and that are known to contribute to age-related diseases. For example, mental disorders are characterized by early-onset chronic inflammatory problems and immune dysfunctions. Most mental disorders are heavily co-morbid with obesity and with metabolic dysfunctions. Individuals who have mental disorders tend to neglect their health, through health behaviors such as poor diet, physical inactivity, and tobacco smoking, and many individuals with mental disorders are socially isolated. And of course, by definition, mental disorders involve dysfunction of the brain. It has been shown that many mental disorders result in neurodegeneration. Links between early-life mental disorders and Alzheimer's Disease and Related Dementias are starting to be reported. In one cohort, participants who had greater histories of psychiatric illness showed significantly faster pace of biological aging from young adulthood to midlife (Moffitt and Caspi, JAMA-Psychiatry, 2019). A key question is how much the connection from psychiatric history to accelerated aging represents a causal process. Behavioral and social scientists can test the hypothesis that mental disorders cause accelerated biological aging, and can rule out alternative explanations to causation, in the context of longitudinal studies. One opportunity is to test whether biological aging slows in response to psychotherapeutics, by incorporating biomarker measures of the pace of

aging into randomized trials of mental health treatments (Moffitt et al., Development & Psychopathology, 2013). A successful mental-health treatment should retard age-related progression on outcomes such as brain age, cognitive processing speed, gait speed, facial aging, and epigenetic aging. More research is needed to clarify the mechanisms that connect psychiatric history to reduced health span.

Conclusion.

Geroscience has not heretofore incorporated a focus on behavioral or social factors in its agenda on slowing aging to extend health span. This absence is natural because geroscience has been intent on researching fundamental mechanisms of aging at the molecular and physiological level, primarily in animal models. Geroscience has tended to follow a basic-bench-science mode of inquiry where social, emotional, cognitive, and behavioral variables are not typically central. However, as geroscience findings are translated to humans' aging in the 'real world,' a central question will become how the geroscience endeavor fares in relation to these very factors. Slowing aging is possible, but how best to make it feasible? How best to insure it improves the health span of the whole population? How to insure that slow aging is accessible to all, and reduces, not exacerbates, health disparities? Questions will also emerge about how the geroscience agenda affects the economy, population demography, inequality, and bioethics. As these challenges are tackled, now is a very good time to promote participation in geroscience among the disciplines that make up the behavioral and social science research community.

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