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Behavioral and Social Research to Accelerate the Geroscience Translation Agenda

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Abstract

Geroscience is the study of how to slow biological aging to extend healthspan and longevity. Geroscience has not heretofore incorporated behavioral or social-science methods or findings 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. This article recommends some ways in which geroscience can be augmented through collaboration with behavioral and social science to: accomplish translation from animal models to humans; inform the design of clinical trials of anti-aging therapies; develop outcome measures for evaluating efficacy of anti-aging therapies, and reduce and not exacerbate health disparities.

The geroscience hypothesis.

Geroscience is the study of how to slow aging to extend healthspan. It has not heretofore incorporated behavioral or social research in its agenda. Instead, 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 require collaboration between geroscientists and behavioral/social researchers. 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 healthspan, 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,

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simultaneously (Barzilai et al., 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 organ-damage 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, 2017).

How might behavioral/social research augment this exciting geroscience agenda? Behavioral/social science, which comprises neuroscience, psychology, demography, sociology, economics, and ethics, is well-situated to contribute to geroscience. It offers research designs such as longitudinal cohort-studies that are ideal for testing change with age, and it also incorporates biological measurements (e.g., biomarkers, genomics, neuroimaging). Sections below will suggest that behavioral/social science is necessary: (a) to accomplish translation of geroscience findings from preclinical animal models to human population health, (b) to inform the design of strong clinical trials of anti-aging therapies, (c) to develop outcome measures for evaluating anti-aging therapies, and (d) to study how the geroscience agenda can reduce and not exacerbate health disparities. This article alerts both geroscientsts and behavioral/social scientists to new scientific opportunities.

Translation of geroscience: The so-called leap from lab to life will require understanding of behavioral and social causation in human aging.

Therapies to extend healthspan are poised to make the move from cellular, molecular, and genomic studies and laboratory animal models to human clinical trials (Tchkonia and Kirkland, 2018). However, 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. This article aims to inform geroscience that translation from mouse to human will entail challenges that might not have been anticipated, arising from the multifactorial heterogeneity of human aging. Aging in laboratory non-human animals under controlled circumstances is not only different from aging in humans, it is even different from aging in free-ranging non-human animals who live under non-laboratory natural conditions. In recognition of this gap, geroscientists are studying domestic dogs (http://dogagingproject.com/). However, compared to aging in laboratory animals and domestic pets, human aging has many more heterogeneous multifactorial origins and influences; behavioral/social in addition to cellular. 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, stress, early-life adverse experiences, or even psychiatric history, which predicts early mortality (Crimmins, this issue; Epel, this issue; Moffitt and Caspi, 2019). Humans vary widely on such factors, and this variation generates differences between individuals in the pace at which they age. Individual differences in the causes of peoples' aging will complicate translation by muting the effect sizes of treatments, thus requiring very large samples for geroscience clinical trials.

A human adult's pace of biological aging may be sped or slowed by familial genetic endowment, by varying early-life experiences and exposures (such as to pollution toxicants), and by individual differences in a number of lifestyle factors that do not characterize laboratory animals, such as diet, physical activity, sleep, mental health, 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 behavioral/social personal-history characteristics present in their childhoods. Adverse experiences, social-class, health, cognitive ability, and self-control, all measured in childhood, predicted differences between individuals in their pace of aging two decades later, and did so over and above prediction from grandparents' longevity. Participants who accumulated more of these psychosocial personal-history risks showed a faster pace of biological aging over the decades it was tracked (Belsky et al., 2017). Human-relevant factors like these have not been studied in geroscience's animal models. However, much human observational research shows that early-life behavioral/social risk factors can statistically predict hard aging endpoint outcomes such as the timing of late-life disease onset, as well as early mortality (Crimmins, this issue).

To assist geroscience translation, behavioral/social research needs to push harder to test whether these predictive associations are, in fact, causal. Behavioral/social scientists should do more to apply research designs to augment causal inference. For example, do twins who are discordant for behavioral/social risk exposures age at different rates? Does biological aging speed up from before to after participants' exposure to behavioral/social risks in longitudinal studies that use the self as one's own control? Does biological aging slow in response to randomized trials of behavioral/social interventions? Behavioral/social factors that causally influence the pace of aging must be better understood because they will inevitably complicate translation of geroscience findings from preclinical animal models to human anti-aging therapeutics. For example, drugs that slow aging in animals tend to target one or more of the cellular hallmarks of aging, but in humans behavioral/social factors also explain variation in aging. It is unknown if aging that is accelerated by behavioral/social factors will respond to cellular-derived treatments, whether behavioral/social and cellular causes have additive versus interactive effects, or how behavioral/social causation is mediated at the cellular level.

It has been remarked that people do not 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 geroscience treatment 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/social epidemiological research in the context of population-representative cohorts can undertake this work.

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 healthspan. An anti-aging pill would be easier to take than a caloric-restriction program. Even so, patients commonly fail to follow prescription-medication regimens properly, and sustaining adherence is a major barrier in all pragmatic trials. Non-adherence is known to be strongly predicted by patients' behavioral/ social characteristics. However, many writings about the promise of geroscience overlook the challenge of adherence, apparently assuming that the reward of longer healthspan will guarantee adherence (Walter, 2020). Furthermore, the same behavioral/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 education, low conscientiousness, and cognitive dysfunctions, among others. By the end of a randomized trial, this situation may re-introduce the bias and confounding that random assignment to trial arms was intended to eliminate (Demets and Cook, 2019). Adherence confounding can be avoided by intention-to-treat (ITT), but unfortunately only one-quarter of trials follow ITT, according to a survey of 2,349 trials (Abraha et al. 2017). For this reason, the marked heterogeneity in causal influences on humans' aging will probably complicate and even compromise clinical trials of anti-aging therapies.

Finally, behavioral/social research will need to inform the implementation science that will span the wide gap between having an anti-aging treatment that looks promising and having an anti-aging treatment that actually improves the health of the population. Even the most effective treatment 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 anti-aging therapies don't work for everyone? These are behavioral/social questions that call for collaboration between geroscientists and behavioral/social implementation scientists.

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., 2015; Tchkonia and Kirkland, 2018). But an obstacle blocks the translational pipeline: a lack of technology to measure the pace of aging in young-to-midlife 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., 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 barrier

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 and unfeasible. 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, 2017).

Work to develop such measures is well underway. It may seem surprising that this work is emerging from behavioral/social science. However, developing measures of human biological aging is inherently research that tracks biological changes over the course of years, and tests whether putative measures of aging can predict future mortality. Many longitudinal cohort studies that were designed to track change and test prediction originated in behavioral/social science, and these studies are well suited to building and validating measures of biological aging. These multidisciplinary behavioral/social cohort studies include the American Health and Retirement Study and cohorts from Britain, Scotland, and New Zealand. For example, in behavioral 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 scan (Cole and Franke, 2017; Cole et al., 2018). In longitudinal research, brain age is related to the pace of biological aging and to cognitive decline (Elliott et al., in press).

As another example of aging measures for young adults, 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 and Raj, 2018). However, there are 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., 2017; Zhang et al., 2019). A key difficulty is that most clocks have been trained on date of birth in samples of people who have varying birth years. A long-established principle in the science of human development is that findings from cross-sectional comparisons between groups of individuals with different birth years do not guarantee findings about longitudinal developmental aging within the same individual over time (Schaie, 1967). Compared to participants with recent birth years, participants with earlier birth years also had more early-life exposure to childhood diseases, toxins such as tobacco smoke and airborne lead, lower-quality nutrition, less education, and had less exposure to antibiotics and anti-inflammatory medications. Each of these exposures may alter the methylome. This means that the assumption that methylation in participants of earlier birth years (i.e. older chronological age) results from and represents their advanced biological age is not wholly correct.

As a result, to measure true age-related decline, studies are needed within the same individuals using multi-wave repeated measures of biomarkers. These studies will emerge from longitudinal cohorts. In one population-representative one-year birth cohort, a multi-biomarker panel of aging-sensitive measures has been tracked with repeated measures at ages 26, 32, 38 and 45 years, yielding an index of each participants' pace of aging that

represents the actual pace of biological decline 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., 2015), as well as to slower gait speed (Rasmussen et al. 2019) and thinner cortex of the brain (Elliott, et al. in press). Further, in a randomized controlled trial, caloric restriction disrupted a multi-biomarker measure of biological aging (Belsky et al., 2017). There is initial proof of principle for an epigenetic DNA-methylation signature that captures decades of within-individual biomarker aging in one blood test, measuring how fast an individual has been aging, not just when they were born (Belsky et al., 2020).

Methods to measure the pace of aging in humans who have not yet developed chronic disease would make it possible to record and quantify, in turn, pre-treatment baseline, during-treatment change, and post-treatment outcome, for participants in randomized clinical trials of anti-aging therapies. A 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. Theragnostic measures that are 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.

Humans' pace of aging may influence their response to treatments. 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 (or unusually treatment-responsive). Randomized clinical trials are obliged to register in advance participant characteristics that will be analyzed as potential moderators of treatment outcome. Information about each trial participant's pace of aging prior to the trial could potentially improve trial design and pre-registration, by allowing planned study of this potential moderator variable to maximize chances of success. Overall, to enhance the translation of novel anti-aging intervention strategies for humans it will be necessary to know what factors, including behavioral/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. Measures must be developed to allow research into these possibilities.

Improved healthspan will not be merely a matter of the absence of disease. However, to date, the race to develop outcome measures for geroscience clinical trials of anti-aging therapeutics has focused on biomarkers (Ferucci, 2019), and has not included measures of cognitive or social aging. Enhanced population health must include more years of sustained intellectual vigor, social participation, physical function, and wellbeing. It should not be assumed that because a treatment causes a person's biomarkers to decline slowly and remain young, their cognitive, social, and behavioral outcomes will remain young as well. In fact, not much is known about how measured biological aging relates to measured social and behavioral aging. Many clinicians know an older-adult patient whose cognitive and social functioning are notably impaired, while their bodily health remains relatively robust. Behavioral/social scientists should act to ensure that not only biomarkers, but behavioral,

cognitive, functional, and social outcome measures are included as outcomes in clinical trials of anti-aging therapeutics.

Geroscience and health disparities.

Health disparities is the term used to explain that healthspan, quality of life in later years, and mortality tend to vary by income, education, occupation, urban-rural residence, race and ethnicity, sex, gender, and sexual orientation. Yet, it cannot escape notice that those most invested in the geroscience agenda so far tend to be from groups that are socially advantaged (Walter, 2020). The geroscience agenda needs to be integrated with the health disparities agenda, to reach beyond the privileged few. To demonstrate the benefit of potential anti-aging treatments for improving the health of the less-privileged 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, prejudice, and other sources of health inequality, because these are the people who age fastest and die youngest. Disadvantaged groups need anti-aging therapeutics most. Trials evaluating anti-aging therapies must effectively represent populations who are most in need of anti-aging therapies for improving health-span, and must recruit participants in numbers sufficient to support statistical power for analyses. Behavioral/social science tools can be applied to improve understanding of basic biological processes of aging in health-disparity groups, and to augment the recruitment of disadvantaged disparity groups into clinical trials. The National Institute on Aging promotes such work on inclusion (https://www.nia.nih.gov/research/osp/framework; NIA PAR-18-749: Examining Diversity, Recruitment and Retention in Aging Research).

Conclusion.

Geroscience has not heretofore incorporated a focus on behavioral or social factors in its agenda on slowing aging to extend healthspan. 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 social, emotional, cognitive, and behavioral factors. Slowing aging is possible, but how best to make it feasible? How to measure slowed aging in young-to-midlife trial participants? How to ensure that slow aging is accessible to all, not just the privileged, 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 the ideal time to promote participation in geroscience among the disciplines that make up the behavioral and social research community.

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