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Roadmap

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A roadmap for conducting more inclusive research on brain resilience in ageing and dementia

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Abstract

The variability in cognitive and brain ageing trajectories may be influenced by inter-individual and community-level differences in resilience that result from differential exposures to social and structural determinants of health and be affected by an individual's sex and gender. However, no clear guidance exists on how to best integrate these diversity-related factors (that is, sex, gender and social and structural determinants of health) into clinical and cognitive neuroscience research on resilience in ageing and dementia. The international Brain Resilience and Diversity in Aging and Dementia (BReDAD) Collaboratory was established in 2024 with the goals of synthesizing knowledge, identifying knowledge gaps and developing recommendations for conducting more inclusive research on resilience in this area. On the basis of a focused review of the literature, and discussions held and recommendations made by the Collaboratory, in this Roadmap article, we present a way forward for integrating diversity in future resilience research. This proposal comprises: (i) developing trust and meaningful long-term relationships with communities historically excluded from research; (ii) diversifying who is engaged in all aspects of the research process; (iii) adopting a life-course perspective; (iv) improving and expanding research designs and measurement tools; and (v) using sensitive computational analytics and mixed methods for testing complex, intersectional models. We conclude by recommending a transdisciplinary approach in resilience research to better reflect the complexities inherent in studying diversity and developing precision medicine outcomes.

Sections

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Introduction

Ageing is associated with an increased risk of cognitive decline and dementia. However, there is considerable variability in cognitive performance levels, slopes and the clinical endpoints of cognitive and brain ageing across individuals and communities[1–4]. For example, an online longitudinal cognitive study[5] tested a cohort of 59,703 individuals aged 18–90 years and found an increase in performance variance with ageing. Although it is possible that age differences in computer literacy[6] may have contributed to these findings, a large body of literature has reported increased inter-individual variability in cognitive performance and brain health with advancing age[7–10]. In addition to inter-individual variability in cognitive performance, some research has reported differences in ageing trajectories and dementia risk at the community level. For example, in the USA, Black and Hispanic people and individuals from other communities who have experienced historical marginalization have a higher prevalence of dementia than those from non-marginalized communities[11–13]. There is also a higher prevalence of Alzheimer disease (AD), the leading cause of dementia, in women/female individuals than in men/male individuals[14] (the sex and gender terminology used in this article are defined in Box 1). However, it remains unclear what factors contribute to these observed community-level and sex and/or gender differences in neurocognitive ageing and dementia prevalence.

It has been proposed that some observed variabilities in cognitive and brain ageing trajectories may be interpreted in terms of individual differences in 'resilience'[15–18]. According to the recent National Institute of Aging (NIA, USA)-sponsored Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia, resilience is a general term that subsumes three brain mechanisms that support cognition and brain function with ageing, namely, brain reserve[19], brain maintenance[20] and cognitive reserve[21] (these terms are defined in Box 2). The working hypothesis is that these mechanisms allow more successful ageing owing to better brain status at baseline (brain reserve), less brain change over time (brain maintenance) and a stronger ability to cope with or compensate for brain changes and the cognitive consequences of brain atrophy, injury or disease that occur differentially with ageing (cognitive reserve)[16].

Many cognitive and clinical neuroscience studies have provided support for how individual differences in brain reserve, brain maintenance and cognitive reserve contribute to the inter-individual variability observed in cognitive function with ageing. For example, longitudinal data from the Second Manifestations of Arterial Diseases Magnetic Resonance (SMART-MR) study[22] revealed that individuals with greater brain reserve (baseline brain parenchymal fraction) and cognitive reserve (higher education and vocabulary) exhibited slower rates of memory decline in late life. In addition, a study[23] reported that exercise may slow down cerebrovascular ageing via its influence on key genetic, molecular and cellular factors that support brain maintenance. Therefore, each of the three mechanisms contributes to resilience in unique ways and can be studied separately in specific studies, depending on the hypotheses being tested. The framework for resilience put forth by the NIA Collaboratory has greatly advanced clinical and cognitive neuroscience models of ageing and dementia risk by providing consensus definitions for these mechanisms.

However, as important as it was, the NIA Collaboratory did not provide clear guidance on how to best integrate considerations of ethnocultural, geographic and sociodemographic diversity (referred collectivity to as 'diversity' here), sex, gender and social and structural determinants of health (SSDH) in clinical and cognitive neuroscience research on resilience in ageing and dementia. SSDH is defined as the conditions under which people are born, grow, live, work and age[24–26], which in turn affect their biological and cognitive health, as well as patterns of change throughout ageing. Accordingly, SSDH includes exposures to social inequities (for example, class and socioeconomic status; discrimination based on race, ethnicity, sex, gender and sexual orientation; and childhood adversity) and institutional inequities (for example, education; access to safe-living environments; and occupational complexity) that are often hypothesized to affect resilience. Diversity, sex and gender are known to influence individual differences in life exposures to SSDH, lifestyle, environmental and biological factors, which in turn are known to influence differential patterns of cognitive and brain ageing[27–29]. Overall, healthy ageing has been associated with synergies among multiple domains (for example, equity, inclusivity, community cohesion, socioeconomics and nutrition). Thus, neuroscience studies of brain health in ageing require greater adoption of interdisciplinary approaches than has been the case to date[30]. For example, differential lifetime exposures to various SSDH factors — such as poorer education[31], lower socioeconomic status[32] and greater social isolation[33] — negatively affect cognitive and brain health with ageing. Similarly, lifestyle factors such as sleep quality[34,35], exercise[23,36] and diet[37,38] also influence brain and cognitive health during ageing. Moreover, Livingston et al.[28] and others[39,40] have noted that most of the research that has contributed to the *Lancet* Commission on dementia prevention, intervention and care has come from high-income countries, and that consideration of risk and resilience factors from low-income and middle-income countries is needed to develop a more inclusive and equitable model of brain health in ageing and dementia risk. Within cognitive and clinical neuroscience research on resilience (Box 2), emerging studies have addressed the influence of some SSDH factors on resilience by sex, gender and other diversity characteristics[41–44]. However, much remains unknown about how differential exposures to SSDH factors across diverse global regions and local communities interact with sex and gender to affect resilience, placing some people at increased or reduced risk of poorer (and declining) brain and cognitive ageing outcomes[27,45]. For example, the increased risk of dementia in people from historically marginalized communities may be related to negative exposures to SSDH, which in turn affects health and resilience with ageing. Similarly, the higher prevalence of AD in women/female individuals may potentially be influenced by the higher rate of socially gendered life experiences in women than in men (that is, caregiving, child rearing and having lower socioeconomic status and lower education)[31,46,47], as well as sex[48–50] and sex differences in risk factor exposure[1,51]. Notably, there is some overlap in the SSDH experienced by women and by people from historically marginalized communities, which raises the possibility of a double jeopardy for women from such communities. However, to date, there is a marked knowledge gap regarding how diversity, sex, gender and SSDH combine to influence brain mechanisms and cognitive evidence of resilience. In addition, these variables all intersect in their causation; however, considerations of intersectionality in cognitive and clinical neurosciences of ageing and dementia are lacking. Intersectionality is defined as the examination of the "dynamics of differences and sameness" across identities[52]. Within the context of human research on resilience in ageing and dementia, we define intersectionality as the autonomous and interactive influences of individuals' identities, SSDH and exposures to non-modifiable and modifiable risk factors for dementia on brain and cognitive health. Birth cohort effects may also contribute to how sex, gender, SSDH and exposures to modifiable risk factors for dementia influence resilience in ageing. For example, past work has shown that

Box 1 | Sex, gender and diversity-related terminology

In this Roadmap article, the term 'sex' is used to refer to sex as a biological variable that influences physiological and physical characteristics of humans and other animals, such as hormone levels and function, reproductive anatomy and chromosomes[122,123]. In human studies, sex is generally used to refer to the sex an individual is assigned at birth. Thus, 'female individuals' and 'male individuals' are used here to refer to people assigned to be female and male, respectively, at birth. The terms 'female' or 'male' are used when discussing sex effects reported in animal studies too. The concept of gender encompasses the societal roles, behaviours, expressions and identities of individuals, which are shaped by social constructs rather than biological sex alone[124,125]. Here, the terms 'women' or 'men' are used when referring to gender effects. As the influences of sex and gender on brain health are often interactive, the terms 'women/female individuals' and 'men/male individuals' are used when it is unclear whether an effect pertains to gender and/or sex. Importantly, there are known variations in how sex as a biological variable is expressed physically and physiologically and in how gender is experienced[126]. Thus, we note the limitations in the use of these binary classifications in this paper and in past studies.

In this article, 'diversity' refers to individual differences in ethnocultural, geographic and sociodemographic backgrounds. In reviewing papers that examined racial and ethnocultural differences in brain health and ageing, we use the terms as stated in the original source material.

higher levels of education are more beneficial to the cognitive and brain reserves of older women than men[31]. However, as more women than men attain higher education in some countries[53], gender differences in educational effects on cognitive and brain reserve may either diminish or invert over time if current educational trends continue.

To address this knowledge gap, an international Brain Resilience and Diversity in Aging and Dementia (BReDAD) Collaboratory was formed, sponsored by the Canadian Institutes of Health Research, Institute of Aging. The overarching goal of the BReDAD Collaboratory is to use a transdisciplinary approach and integrate theories, methodologies and applications from complementary research fields – cognitive and clinical neuroscience, geriatrics and gerontology, neurology, biology, epidemiology, computational neuroscience, sex and gender science, as well as sociology and other cultural and social sciences – to enable more equitable and inclusive research on resilience in ageing and dementia. Thus, the BReDAD Collaboratory includes members from diverse academic backgrounds (see Supplementary Information). To meet this goal, contributions and experiences from outside acadaemia are also needed. As such, the Collaboratory also includes (i) knowledge users (KUs) with direct connections to diverse community-dwelling older adults and (ii) persons with lived experiences (PWLEs), including people with dementia and carers.

In this Roadmap article, we first summarize the knowledge synthesis activities of the BReDAD Collaboratory. Subsequently, we provide a way forward for advancing a more inclusive understanding of resilience by integrating considerations of diversity and intersectionality into research on resilience in ageing and dementia.

What is known and what remains unknown?

Diversity, SSDH and resilience

There is some evidence that the differential prevalence rates of dementia and age-related cognitive decline across ethnocultural, geographic and sociodemographic communities may be due to differences in lifetime exposures to modifiable risk factors for dementia, which in turn affect resilience and cognition. Modifiable risk factors are defined as behaviours or exposures that can be changed to help prevent and/or delay dementia in individuals[54], and exposures to these risk factors may vary with SSDH. Modifiable risk factors may act on brain and cognitive health at midlife (for example, hearing loss, obesity, hypertension, depression, traumatic brain injury, diabetes, smoking and excessive alcohol used) and/or later life (for example, social isolation, air pollution and vision loss)[28]. For example, in the USA, midlife obesity was associated with a greater risk of developing AD in Black, American Indian and Alaska Native people than it was in White people[55] (Box 1). Another study from USA found that depression was less often diagnosed in Black and Hispanic people than in non-Hispanic White people, possibly owing to a reduction in health-care access; however, when depression was diagnosed in these communities, it was linked to more marked, negative outcomes relating to age-related differences in brain health and cognition[56]. Age-related sleeping difficulties also seem to be associated with poorer brain health and cognition in Black people than in White people in the USA[57,58]. Thus, there is some emerging work from the USA indicating that individuals from historically minoritized and/or racialized backgrounds may have greater exposures to modifiable risk factors for dementia and, in turn, experience poorer cognitive and brain health with advancing age.

What is less clear is how exposures to modifiable risk factors affect the underlying resilience mechanisms of brain reserve, brain maintenance and cognitive reserve and, moreover, whether these effects are the same across diverse communities. One possibility is that exposure to some modifiable risk factors (for example, hypertension, diabetes and traumatic brain injuries) may cause neuropathology and reduce the availability and effectiveness of resilience mechanisms[54]. By contrast, exposures to positive health modifiers (for example, exercise and socialization) may support the effectiveness of resilience mechanisms. Importantly, increased exposures to modifiable risk factors in diverse communities that are marginalized may be proxies for SSDH. Therefore, research on ethnocultural, geographic and sociodemographic differences in resilience and dementia risk should consistently examine whether SSDH factors act as mediators or moderators of racial and ethnic group differences in cognitive and brain ageing, risk for AD and resilience. However, to our knowledge, there have been no studies explicitly exploring how SSDH and the presence or absence of modifiable risk factors affect brain health and cognition in ageing and dementia across diverse communities. This lack of knowledge needs to be addressed to counter extant health inequities in dementia prevalence rates in historically underserved and diverse communities.

Studies of communities historically excluded from research have mostly focused on studying modifiable and non-modifiable risk factors of cognitive decline and/or dementia, in an aim to explain the higher prevalence of dementia in some of these historically excluded communities. However, little is known about whether there are community-specific resilience mechanisms that support cognitive function with age or in the presence of dementia risk factors in more diverse cohorts. Therefore, there is a need to take a more balanced

approach to understanding brain health in ageing and dementia in diverse communities, so that diversity is not equated with adversity and vulnerability. There may be unique modifiable and non-modifiable resilience factors that support healthier ageing in communities historically excluded from research, and future work should focus on identifying risk and resilience factors that may be novel and community-specific.

Sex, gender and resilience

When approaching resilience research in diverse, under-represented communities, it can be enlightening to turn to an area of diversity in which more research has been conducted: sex and gender research. In the past, sex and gender differences in brain health and ageing could not be studied because women and female individuals were sorely under-represented in clinical studies, as were female animals in non-human animal research. However, in the past 20 years, a concerted effort through research, publications, conferences, political lobbying and funding initiatives has increased the presence and exploration of the unique features of sex and gender in human health[59–61].

The field of sex and gender science has been addressing many of the same issues currently faced by diverse, historically marginalized communities in brain research: inclusion in studies, studying the person-appropriate factors and analysing for complexity. For example, most resilience research has been carried out either in male animals or without disaggregating analyses by sex and/or gender in human studies. Owing to this, a vast literature exists in which sex differences have been obscured either because only male individuals were studied or because sex was controlled for during data analysis. For example, although more women/female individuals than men/male individuals are diagnosed with AD, the reason for this sex and/or gender difference in prevalence remains unclear[49,62].

A recent narrative review[41] summarized sex and gender differences in cognitive ageing and AD. It reported that women and/or female individuals with mild cognitive impairment (MCI) progressed faster to a dementia diagnosis than did male individuals/men, and that this may reflect a sex difference in resilience to MCI pathology. In addition, there is a higher prevalence of the apolipoprotein E ε4 (*APOE ε4*) genotype (a known non-modifiable risk factor for AD) in female individuals diagnosed with AD than in male individuals diagnosed with AD, and *APOE ε4*-carrying female individuals diagnosed with MCI or AD exhibit poorer episodic memory than male individuals with the same genotype[41,63,64]. Episodic memory decline is a hallmark symptom of dementia, and AD in particular[65]. However, cognitive ageing studies of healthy adults have consistently shown that women/female individuals perform better than men/male individuals on episodic memory verbal tests throughout the lifetime[66]. Thus, the poorer memory performance observed in women/female individuals with MCI or AD than in men/male individuals is noteworthy and points to a marked sex difference in cognitive decline and resilience in the context of age-related versus dementia-related episodic memory decline.

At the neural level, few studies have explored sex and gender differences in resilience mechanisms, and the findings that are available are inconsistent, owing to differing outcome measures and definitions of resilience[41]. However, some data suggest that women/female individuals may show lower resilience to some types of AD neuropathology (cerebral tau levels and hippocampal atrophy) but not others (amyloid-β levels in the brain)[41,49,67]. Emerging data also suggest that compared with men/male individuals, some women/female individuals exhibit a steeper rate of episodic memory decline at late midlife and older age as a function of how they experience menopause and whether they have high levels of vascular risk factors, such as hypertension[68–70]. However, no study has clearly examined how sex and/or gender affect all resilience mechanisms in the brain. Therefore, much is still unknown about sex differences in resilience and ageing, with even less known about gender differences — both gender identification and gender as social norms. Regarding the latter, Arenaza-Urquijo et al.[41] urged a flexible multidisciplinary approach in which the focus is on understanding

Box 2 | What is resilience?

General theories of resilience have influenced education, psychology, biology and many medical fields since the early nineteenth century[18]. With regard to resilience in ageing, in 2003, McEwen and Stellar[107] proposed a biological stress model of resilience in ageing, in which they hypothesized that individual differences in immune, autonomic and neuroendocrine system functions mediated differences in allostasis (the ability of an organism to maintain homeostasis), and that the former were the basis of variability in brain resilience with ageing. In this model, brain resilience was defined as the ability to maintain healthy levels of brain structure and function in the presence of chronic challenges to allostasis that occur with ageing.

More recently, the National Institute of Aging (USA)-funded Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia developed a framework for concepts of reserve and resilience in ageing[15]. In this framework, resilience is characterized as a general term that subsumes three mechanisms that support one's ability to maintain effective levels of cognition and brain function during ageing. The first of these is brain reserve[19], which is defined as the neurobiological status of individual's brain structure (as opposed to brain function) at a point in time that is relevant to cognition. The second is brain maintenance[20], which is defined as the relative absence of changes in neural resources or neuropathological changes over time as a determinant of preserved cognition in older age. This refers to individual differences in the development of age-related structural changes, neurodegeneration and dementia-related neuropathology, for example, amyloid plaques and neurofibrillary tangles in the case of Alzheimer disease (maintenance has been sometimes referred to as resistance by others)[14,17]. The third mechanism is termed cognitive reserve, defined as a property of the brain that enables cognitive performance that is better than expected given the degree of life-course-related brain changes and brain injury or disease. At the neural level, cognitive reserve may be instantiated via greater neural efficiency or capacity in the utilization of brain regions and networks, and a greater ability to functionally compensate and flexibly engage neural systems not commonly engaged to perform a given task, to enhance performance[20–22]. Notably, the NIA-funded Collaboratory hypothesized that (i) all aspects of resilience are influenced by differential exposures to enriching or detrimental life experiences and social and structural determinants of health[15,21]; and (ii) systematic patterns of such differential exposures may lead to substantial differences in brain reserve, brain maintenance and cognitive reserve.

the interplay among biological and social factors differentially associated with the emergence of specific expressions of resilience. Such an approach would contribute to resilience research in diverse communities that comprise women and men with various intersectional identities.

It is also noteworthy that sex and gender have often been treated monolithically. For example, sex-based human and animal models do not adequately represent the nuances of how social factors and daily life shape women's and men's biology. This monolithic approach to women and men has impeded our understanding of their range of resiliencies. Not studying how sex and gender interact with other diversities (that is, ethnicity, socioeconomic status and so on) will affect the success of developing a deeper understanding about the resilience of individuals with intersectional identities.

There has also been resistance to women-only and female individual-only studies, which has left serious gaps in our knowledge about the diversities of brain ageing in women and female individuals[47]. For example, for too long we have assumed that all menopauses are the same and studied them together; however, some types of menopause carry a greater risk than others for dementia and poorer cognitive ageing[71]. Female individuals who experience surgically induced menopause following the removal of their ovaries (oophorectomy), or premature menopause before the age of 40 years, have a greater risk of cognitive decline and dementia in older age[71]. By contrast, some evidence exists that pregnancy might confer resilience in brain and cognitive ageing in female individuals, but the benefits depend on the number of pregnancies experienced, age of first pregnancy and other factors that covary with some SSDH[72,73]. Thus, studying one sex is important to reveal the diversities present within a group. Similarly, within race, ethnicity and cultural studies, examining intersectional identities is important for understanding how the diversity of identities affects brain resilience in ageing. For example, when the intersection of race and gender was explored, it was found that Black women had more severe memory and visuospatial declines than non-Hispanic White women[74]. Such findings underscore the importance of studying distinct populations and taking an intersectional approach to sex and gender.

Methodological considerations

Advances in research on resilience in ageing and dementia have emerged within cognitive, neuroscience and epidemiological disciplines[15,64,66,75]. The subsequent integration of sex, gender and diversity will require resilience researchers to address novel conceptual challenges and engage in methodological opportunities. For example, some adaptations may be required in resilience nomenclature, conceptual frameworks, operationalization approaches and even data collection and analysis strategies[34,66]. Such adjustments have been considered in broader epidemiological and comparative ethnocultural contexts of ageing and dementia research[76,77]. For example, Livingston et al.[28] noted that brain health-related and dementia-related life-course risk factors and adversities may be not only more prevalent in some ethnoculturally and demographically diverse groups, but also exacerbated in their intensity and interactive potency by prevailing and differential SSDH, as well as differences in precision measurement characteristics[78]. For communities with elevated SSDH exposures, such adversities are likely to occur in multiples with moderating (not solely independent) effects. Accordingly, in studies designed to accommodate these challenges, precise methodological adaptations are required. Early examples have included sex-sensitive and gender-sensitive approaches to operationalizing resilience as related to ageing and specific adversities, such as those used in studies of diverse communities, including older Black and White people in the USA[42] and women/female adults and men/male adults[43,44]. Regarding the latter, a recent comprehensive review of sex and gender differences in resilience suggested a focus on understanding how biological, social and cultural factors that are differentially associated with the emergence of specific expressions of resilience interact, and proposed a multidisciplinary, flexible approach[41]. Such critical reviews and methodological adaptations will contribute to resilience research in ethnoculturally, geographically and sociodemographically diverse communities that include both women/female individuals and men/male individuals as well as the intersection of multiple biological aspects of sex and the sociocultural facets of gender.

It is also critical to consider sex, gender and various intersectional profiles when studying dementia risk and resilience globally and in diverse communities[79]. For example, accumulating longitudinal research shows that ageing women/female individuals and men/male individuals progress through cognitive and brain ageing (and towards or away from dementia) differently[41,80]. To meet the resulting methodological challenge, diversity-sensitive research on resilience should collect data on people of different sexes and genders and disaggregate analyses by sex and gender. In addition, it is important to conduct more in-depth phenotyping of sex-specific experiences and gender-related SSDH factors. This includes assessing numerous novel factors and conditions, including: sex-related and gender-related factors (for example, changes in reproductive hormone levels[81]), the number of pregnancies completed, type of menopause[82,83], gendered life circumstances leading to increased risk[84] and allostatic load (stress)[85,86], along with their interactions with non-modifiable risk factors for cognitive impairment and AD (for example, *APOE ε4* allele carrier status)[41]. Researchers are encouraged to consider that sex and gender may interact with other dimensions of diversity that, on their own, affect cognitive and brain ageing trajectories. The use of comprehensive measurement approaches and multiple disciplinary designs and analytic approaches are critical for advancing a more detailed, nuanced and intersectional approach in resilience research.

In summary, conceptual developments and research activities pertaining to resilience in ageing and dementia are flourishing[15,34,64,66]. However, various methodological challenges have emerged when researchers have included dynamic, differential and interactive complexities associated with ageing and dementia in diverse and intersectional communities. Among these challenges are the quality of data in all aspects of the research, including health inequalities, community characteristics and national trends[87,88]. Specifically, cognitive health and resilience patterns can be markedly influenced by differing life-course exposures to risk and protection factors, as well as community-wide disparities in access to social and structural supports for ageing health. Key methodological recommendations include the following. First, studies of resilience in ageing and dementia can be enhanced by expanding the heterogeneity of the research samples and studying multiple dimensions of diversity and their interactions[34,35]. Second, conceptual and operational definitions of resilience are often dynamic, such as representing contrasting change profiles over long periods of life[2,4,36,37]. Deploying time-structured data collection procedures (such as longitudinal designs) accompanied by change-sensitive analytics can deepen our understanding of ageing-related and dementia-related resilience within and across diverse communities. Third, people within a community may express differential responsivity to adversities, inequities and their interactions at any given point

and over time. Fourth, including dynamic and interactive resilience research questions may require correspondingly sensitive quantitative and/or qualitative analytical tools. Computational techniques are becoming broadly available through developments in AI (such as machine-learning longitudinal models) as well as the growth of user-friendly and expert-supported data processing packages. Fifth, when heterogeneity methods have been incorporated in brain ageing and dementia research, alternate forms or even subgroups of participants are often detected[75,89], sometimes in surprising phenotypic combinations. Finally, the detection of precisely defined subgroups of persons with complementary characteristics — often through change-sensitive designs and data-driven analytics — is of growing interest in ageing and dementia[86]. Through considering a wider range of diversity-related factors that influence the heterogeneous pathways of ageing, resilience researchers can advance our understanding of common clinical conditions and promote precision interventions for healthier brain and cognitive ageing.

A roadmap for integrating diversity in research on resilience in ageing and dementia

As documented earlier, there are formidable deficits in our current knowledge about the cognitive and brain health status of ageing individuals from historically marginalized communities and challenges for efforts to expand our knowledge by integrating multiple aspects of diversity with novel methodological approaches in brain ageing and dementia research. The review of the literature presented here and ongoing discussions in the BReDAD Collaboratory have led to the development of a roadmap, presented subsequently and summarized in Fig. 1, that provides guidance on procedural and methodological ways to integrate sex, gender, diversity and SSDH in research on resilience in ageing and dementia[30,90]. As displayed in Fig. 1, we conceptualize and display this roadmap as a dynamic set of five nested, interdependent characteristics or 'roadways', all of which are essential for advancing an inclusive and representative understanding of resilience in ageing and dementia. The roadmap is temporal in that the goals and procedures are represented as unfolding over time, as are the processes of brain and cognitive ageing that can be used as evidence for or against resilience. We present specific recommendations for researchers to enact and sustain each roadway in resilience research (summarized in the figure for each of the roadways). The five roadways are depicted as dynamically nested with one another so that advances in early roadways will inform and support specific goals, actions, methods and interpretations in others. The roadways are described as interactive in that they merge into a single arrowhead, to reflect a common multi-influenced direction of influence. A provisional outcome of deeply integrating diversity in resilience and ageing research is portrayed as the detection and description of diversity-related forms of resilience — a potential precision outcome for enhancing understanding and promoting healthier brain ageing. In the following paragraphs, we describe the roadmap and present procedural and methodological recommendations for representing each component and enacting them together in resilience research.

Establish long-term and trustworthy relationships

The initial roadway emphasizes the importance of researchers advancing our understanding of how race and racism, diverse identities,

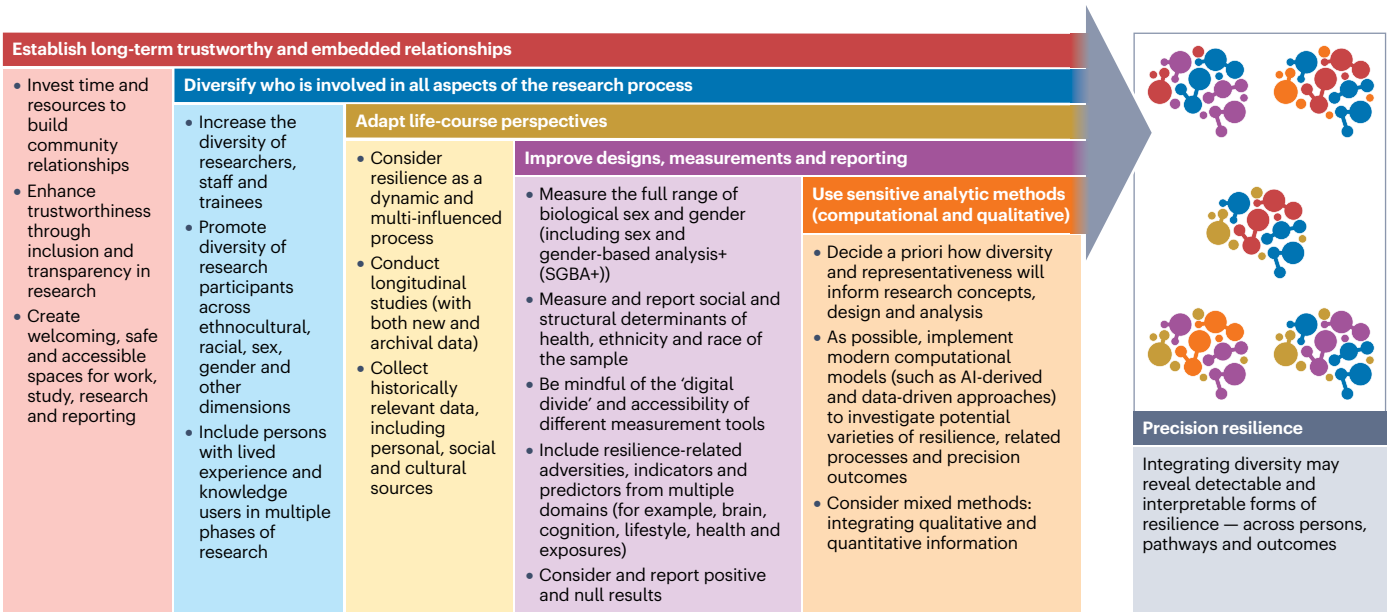

Fig. 1 | A roadmap for integrating diversity in research on resilience in ageing and dementia. The schematic provides a visual representation of the proposed dynamic nested roadmap for integrating diversity in resilience research in the context of ageing and dementia. The roadmap comprises five roadways, which are portrayed as nested components to emphasize that they are mutually essential features of such research. Each of the five roadways is described conceptually and operationally in associated text boxes. The five roadway arrows reflect the 'dynamic' and continuing temporal aspect of research efforts. The single arrowhead represents the synergy produced by the sustained combination of the five roadways. The 'precision' outcome illustrates the possibility of forms of resilience with shared phenotypic characteristics but diversity-related heterogeneity. Such precision outcomes hold promise for developing effective interventions aimed at promoting more resilience in brain ageing within and across diverse communities varying in equity, accessibility and socioeconomic strata. AI, artificial intelligence.

SSDH, sex, gender and their intersections affect resilience in ageing and dementia by increasing the representation of individuals from diverse communities in new or ongoing research programmes (Fig. 1). To achieve this goal, researchers are advised to first engage with individuals from historically excluded communities, build trustworthiness, develop a common purpose and commit to developing long-term relationships that are mutually beneficial. Respectful co-creation of research goals and methods also means that researchers must adapt some of the traditional ways of approaching the scientific enterprise. Such efforts require time, commitment and substantial resources.

A promising approach for building trustworthy relationships is to ensure transparency in communications with community members throughout the research process. This includes being explicit about research goals and hypotheses but also actively inviting suggestions from the communities. For example, researchers should clarify whether their goal is to simply have an inclusive cohort that is representative of population statistics, or to have sufficient statistical power to examine how different communities and identities experience brain ageing and resilience. This is important, because meeting funding agency requirements for demographically representative cohorts may not require the sample sizes that would be needed to advance our understanding of brain ageing and resilience in a historically marginalized community. Indeed, if the aim of the study is to address health inequities and understand resilience in ageing and dementia in communities historically excluded from research, it is critical that researchers ensure that their study is sufficiently powered to address this goal.

Ensuring research spaces are safe, accessible, respectful and welcoming to people from the community of interest is critical. For example, working with communities that have specific accessibility needs will require selecting locations that are inclusive and ensuring that different modes of communication are available to enable equitable participation. Also, the interior design of spaces should be considered. It is possible that settings within academic or biomedical environments might not feel safe or welcoming to some communities. Creating research spaces outside these traditional environments that are designed with community needs and preferences in mind may be one way to make research spaces more accessible and inclusive.

Once trust is built and communities are actively participating in research, it is important to ensure, through consultation with PWLE and KUs, that the study design and testing materials used in research are culturally appropriate and unbiased. Similarly, it is recommended that PWLE and KU involvement in data interpretation be sought to ensure that data are interpreted through an anti-colonialist, health equity lens. In addition, it is critical that there are mutually beneficial policies of community engagement and knowledge mobilization in place that serve the needs of scientists, PWLE and KUs, with research findings being disseminated to participating communities in a timely manner.

Diversify who is involved in all aspects of the research process

Diversifying who is involved in research is another essential component to evaluating health inequity effects and understanding how diversity-related factors contribute to resilience in ageing and dementia (Fig. 1). In some jurisdictions, governmental, institutional and funding agency commitments to increasing the diversity of researchers, staff and trainees will help to create more inclusive recruitment practices, diversify the languages and testing materials used in research and enhance community relationships. For example, if a researcher is working with a South Asian community in which Punjabi is the first language, it would be important to have research team members who could fluently communicate with community members and who have cultural knowledge to initiate and support community engagement. Ultimately, including diverse voices in research will enhance trust, democratize science and lead to the creation of a more representative understanding of what factors support and/or hinder brain resilience in ageing and dementia across communities. In addition, as noted in the roadmap graphic, including PWLEs and KUs on the research team can complement an effectively diverse research group.

Adapt life-course perspectives

The third roadway represents the notion that there are clear benefits for researchers engaged in cognitive, social and clinical neuroscience studies of ageing and dementia to integrate conceptual and methodological approaches featured in related disciplines, such as lifespan or ageing-related areas within developmental and social psychology[23,24] (Fig. 1). For example, some developmental researchers have adapted life-course perspectives to better understand how experiences of discrimination in historically under-represented individuals affect mental health outcomes such as depression[91,92]. Life-course perspectives emphasize the importance of studying how individual, social, contextual and historical factors are integrated to affect an individual's brain, mental health and general health across the lifespan[93–95]. For example, Blazer et al.[94] have argued for a 'life-course epidemiology', in which cultural, social and environmental contexts and individualized exposures can be assessed as interactively influencing brain and cognitive health throughout life. Similarly, Eyre et al.[95] have advocated for a 'holistic' lifespan approach, in which medical, psychological and sociocultural considerations are integrated in empirical research on brain health in ageing, as well as culturally sensitive intervention strategies for promoting healthy brain development throughout life. Notably, in a series of early publications, Baltes et al.[93] articulated a set of concordant perspectives in their lifespan model, promoting complex and long-term longitudinal designs along with multivariable databases reflecting health, social, cultural and historical contexts.

An additional consideration in life-course approaches is that there may be a considerable time lag between exposure to specific SSDH and modifiable risk factors and their effects on resilience; for example, discrimination in young adulthood and midlife and the appearance of impairment or dementia in later life[96]. In summary, it is important to consider a life-course perspective on how earlier life exposures to SSDH and modifiable risk factors may have late-life effects on resilience in ageing and dementia risk.

Improve designs and measurements and refine research questions

The fourth roadway supplements the methodological challenges of improving inclusion and representativeness of 'who is doing the research?' and 'who is participating in research?' (Fig. 1). Specifically, it represents the idea that resilience research on ageing and dementia also needs to refine research questions, enhance research designs and improve measurement techniques to better differentiate resilience-related concepts (for example, reserve, resistance, compensation, maintenance and exceptionality), clarify the relative merits of contrasting operational definitions, proxies and measures of resilience and provide guidance for implementing effective and sensitive research designs within and across multiple communities[16,28,97–99]. Overcoming these methodological challenges to assessment and interpretation will require the integration of methods used across broader comparative ethnocultural contexts[76].

This Roadmap article has used the NIA Collaboratory Framework[16,100] for resilience as a summary term for three distinguishable facets: brain reserve, brain maintenance and cognitive reserve. Researchers should continue to challenge current operational definitions and explore, refine and test alternative definitions for resilience by using the following: psychometric instruments that permit broad assessments of resilience behaviours, affect, and conditions such as adversities and SSDH[90,101]; the often criticized but frequently implemented regression-related 'residual' approach[102,103]; recent novel polygenic (or other composite) resilience score approaches[104]; and a time-structured, within-person approach incorporating an indicator of a shared burden or adversity[44,99]. Consideration of the epigenetic influence of ethnocultural, geographic and sociodemographic diversity-related factors — for example, exposures to specific SSDH such as racism and structural determinants of health — on an individual's resilience also needs further study. For example, Krieger et al.[105] reported that in a large sample of American adults from the My Body My Story (MBMS) and Multi-Ethnic Atherosclerosis (MESA) studies, epigenetic age acceleration was related to individual differences in exposures to racialized and economic injustice. However, it remains unclear how these epigenetic effects relate to individual differences in resilience.

In addition, integrating allostatic load into models of resilience may help to refine and improve measures of resilience in more inclusive cohorts. Allostatic load is a measure of the cumulative effect of repeated exposures to stressful events[106]. It can vary by ethnocultural diversity, exposures to SSDH variables, sex, gender and sexual minority status[86,107]. Allostatic load has been used as a marker of resilience and accelerated ageing[108] and is negatively correlated with cognitive function[109]. Research on sex differences in allostatic load in the adult lifespan has found that younger male individuals have higher allostatic load than younger female individuals; but younger female individuals showed higher gender-specific stress factors associated with age, race, ethnicity, adversities, social support and health behaviours[106]. However, in older couples, allostatic load is lower and does not exhibit as steep an age-related increase in male individuals as it does in female individuals[110]. Allostatic load also varies by sexual orientation and by racialized or minoritized status[111–113]. Thus, one's experience of allostatic load, which in part will be informed by the interacting influences of one's multiple identities and exposures to SSDH, may be a bellwether of risk and resilience in diverse communities. Measurement and integration of allostatic load into models of resilience factors in ageing and dementia might be one promising way to make models more representative and generalizable.

The inclusion of computer and online testing of cognitive function in ageing and dementia research is often implemented to improve access and efficiency in data collection[114–116]. Often, the intention behind implementing these technological solutions is to include larger, more diverse cohorts in research. However, researchers implementing computer and online testing methods must be mindful of the 'digital divide'[6], which may result in confounding computer literacy effects with those associated with age, sex, ethnicity and other diversity-related factors[6,81,82].

Advances in measuring AD blood biomarkers — for example, plasma measures of phosphorylated tau and amyloid-$\beta_{42/40}$ — have increased the number of studies using these methods[117]. On the one hand, AD blood biomarker research is more easily scalable and cost-effective than positron-emission tomography and/or cerebrospinal fluid measures of AD proteinopathies. Thus, it can potentially improve inclusion and diversity of study participants and advance our understanding of how individual differences in AD blood biomarkers affect resilience-related measures of brain reserve, brain maintenance and cognitive reserve. On the other hand, these methods still face challenges in participant buy-in, accessibility and cost. Given the potential of unpleasant encounters with biomedicalized procedures as well as medical and health-care implications of obtaining a positive biomarker result, a high level of trust needs to be established between researchers and historically under-represented and/or marginalized communities before their implementation, given the potential for ethical concerns and possible exploitation by health-care providers and insurers in some countries.

Use sensitive analytical methods

The fifth roadway refers to resilience data evaluation and thus is especially complementary to the fourth roadway (design and measurement) (Fig. 1). It is a crucial characteristic of the roadmap, as it reflects the synergistic combination of all the other recommendations outlined in Fig. 1. Integrating diversity in resilience research on ageing and dementia is represented as involving, at least in some projects, multiple indicators of context (for example, historical, geographical, ethnocultural, sex and gender) and multiple occasions of measurement across a life course. The challenges of how large multidimensional databases are systematically 'mined' — whether quantitatively, qualitatively or both, as in mixed approaches — applies to virtually all research designs. This includes two major designs that are often contrasted: cross-sectional and longitudinal research designs[118]. Although the former design typically compares age (for example, young versus old adults) or clinical groups (for example, asymptomatic versus AD groups) and thus produces legitimate evidence of between-group differences, longitudinal studies typically follow one or more age and/or clinical cohorts over some period of time and thus produce evidence of within-person change, as well as crucial insights regarding between-person differences in within-person change. Both approaches have well-explicated methodological strengths and limitations, and both have attracted recent upgrades in terms of database size, technological sophistication, recruitment and retention techniques and available analytic tools. For this reason, these are complementary approaches to different conceptual aspects and empirical features of resilience. However, some consideration should be given to recent observations regarding the match between dynamic and interactive concepts of resilience and the concordant possibilities inherent in longitudinal designs[104]. In addition, applying artificial-intelligence-derived and data-driven analytics (for example, machine learning) to longitudinal and single-wave big data studies will provide powerful tools for discovery and validation in the heterogeneous pathways and predictors of resilience and non-resilience[8,98]. As noted, qualitative information can be profitably evaluated in either design — and such information and approaches can enhance our understanding of many of the life-course characteristics described earlier.

It is critical when studying resilience across diverse individuals and communities that sociocultural and historical contexts are considered. Researchers must remain mindful to not use one community or phenotype as a norm against which other communities or phenotypes are compared and must remain aware of how data are structured and interrogated. A pivotal point is whether and when a researcher should consider a 'splitting' approach, in which data are disaggregated into subgroups (for example, by sex or ethnicity), or a 'lumping' approach, in which all available data from different diversity groups are analysed together. The former is a viable approach to incorporating diversity

but is most effective when the researcher has ensured that all targeted subgroups are adequately populated (and therefore statistically testable). The latter occurs when available participants from different diversity groups are combined in a single data set and analyses are conducted on the full sample — as though they represented a homogeneous population or with the improbable assumption that including diverse participants is tantamount to studying their identity-related characteristics. Disaggregation can be based on overt person attributes (for example, sex) but may also be accomplished in big data sets through powerful data-driven analytic technologies. These resulting 'discovered' secondary phenotypes or subtypes may be based on a host of person indicators cutting across multiple domains or person characteristics, including dynamic change patterns. In resilience research, these may include person indicators from the biological to the social lifestyle and from relatively internal 'omics' data (genomic, proteomic and connectomic) to relatively external environmental and social structural (exposome) data[89,119,120]. Such integrative perspectives may lead, in turn, to discernable, deployable and precise knowledge applications for promoting more resilient ageing across diverse communities[121].

Conclusions

A growing body of research has explored how diversity, sex and gender affect brain health and cognition in ageing and dementia. However, few of these studies have explicitly examined the effects of resilience, as defined by the NIA (USA)-sponsored Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia. Moreover, no study, to our knowledge, has considered how intersectionality affects resilience in ageing and dementia.

Developing a more inclusive and representative understanding of resilience in ageing and dementia is critical for creating more precise neurocognitive models of ageing and dementia, developing personalized approaches for supporting healthy ageing, discovering new, and more precise, early biomarkers for dementia across diverse communities, and developing individualized and community-sensitive treatments for the prevention and care of dementia. On the basis of the knowledge synthesis activities of the BReDAD Collaboratory, we have developed a roadmap (Fig. 1) that provides five recommendations for advancing more inclusive resilience research in ageing and dementia. These recommendations comprise establishing trust and developing long-term relationships with communities historically excluded from resilience research; increasing the diversity of who is conducting the research; adapting a life-course perspective; improving study design by being more inclusive in methods; and using more sensitive and culturally informed analytic methods.

Taking a more representative and inclusive approach to resilience research will require a transdisciplinary approach, time and considerable resources. Funding agencies and governments need to commit to initiatives that support community co-created cognitive and clinical neuroscience studies that meaningfully engage individuals historically excluded from research. Importantly, studies involving diverse communities often take an adversity perspective and do not consider how these communities may also exhibit unique resilience mechanisms. Future studies should aim to fill this knowledge gap. Only by conducting more inclusive resilience research can we develop precision diagnostics and treatments that will support brain and cognitive ageing across diverse communities.

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