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Making bridges between preclinical and clinical insights into age-related cognitive decline

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With people living longer, the societal impact of age-related cognitive decline is becoming more pronounced (Crimmins, 2015). Thus, it is increasingly important to comprehend the cognitive shifts linked to aging – whether they are physiological or pathological. Neurodegenerative disorders are particularly prevalent in older individuals, as the incidence of these conditions is positively correlated with age. However, gene mutations can accelerate the onset of age-related cognitive decline (Pan et al., 2021). Even individuals without dementia, may experience subtle changes in cognition as they grow older, estimated to affect around 20% of older adults (Pais et al., 2020; Chen et al., 2023). Recognizing these cognitive alterations is essential because they can influence an elderly person's daily functioning and assist in distinguishing between normal aging and illness (Harada et al., 2013). Furthermore, emerging evidence suggests that individuals experiencing age-related cognitive decline without disease exhibit higher rates of hospitalizations and increased risk for adverse effects (Fogg et al., 2018; Amini et al., 2019). Therefore, it is essential to identify the structural and functional changes responsible for these symptoms.

This stresses the need to integrate a variety of research methods to gain a better understanding and effectively address age-related cognitive decline. The elderly are especially susceptible to cognitive function decline. Memory impairments that affect older adults are often attributed to neurodegenerative disorders (Esteves et al., 2023). Even without dementia, there are noticeable age-related alterations in cognitive function leading to a decline of specific types of memories, showing deterioration as early as the fourth decade of life. Prevention of age-dependent deterioration of cognitive function is somewhat depending highly on lifestyle (Rajado et al., 2023). Efforts have also been made to identify biomarkers of early age-related cognitive impairment, with particular focus on markers such as inflammation, neuroaxonal damage, extracellular vesicles, and DNA methylation. These show promise in evaluating the risk of developing cognitive impairment in apparently healthy older adults (Silva et al., 2023; Kerminen et al., 2024). To date, there are no approved drugs specifically designed to treat age-related cognitive decline, as the currently approved medications are primarily targeted towards managing symptoms of dementia.

The use of animal models provides valuable insights into studying age-related brain alterations decline (Brito et al., 2020a, b; Afonso et al., 2022; Koppenol et al., 2023). Currently, there are several common tests used for assessing long-term memory impairments in both humans and rodents (Brito et al., 2024), which proves particularly relevant given that long-term cognitive performance serves as a sensitive indicator of age-related decline.

A study by Brito et al. (2023) reviewed major alterations of the aging brain that are conserved in rodent models and humans, as well as human-specific alterations. For example, they examine how two widely used classifications, crystalized intelligence, and fluid intelligence, are affected by age. The review also discusses the impact of aging on the spatial navigation pattern of humans and mice. These navigation strategies are linked to the vulnerability of specific brain regions during aging, which is thought to result in increased neuronal activity in unaffected brain regions as a compensatory mechanism (Morcom and Henson, 2018). Furthermore, they underscore different memory classifications related to memory endurance: short-term memory, and long-term recall, noting variations between animal mouse models and human subjects during aging.

Next, the authors discussed several obstacles in performing preclinical and clinical research on age-related cognitive decline, such as challenges in performing clinical trials or obtaining specimens from elderly subjects for various reasons. Individuals suffering from this condition often avoid medical intervention because it does not directly cause mortality. Lastly, the development of this condition takes decades of life, which limits the creation and conclusion of clinical trials.

Moreover, the authors highlighted well-established animal models that share with humans many neurological alterations that accompany aging. For instance, variation in neuronal activity in specific brain regions as well as impairments in decreased accuracy in the formation of specific memory subtypes. Some cross-species comparisons are unfortunately not possible given that humans have advanced reasoning and cognitive function that cannot be fully modeled in rodents.

However, many memory types crucial for survival and daily function, such as spatial navigation and spatial memories, which depend on brain structures like the hippocampus show a functional decline during aging in both humans and animal models. Efforts should be made to better link preclinical and clinical research to test and apply findings from preclinical studies to humans.

The neuroscience community has developed robust behavior paradigms over the past 40 years that can accurately detect alterations in cognitive function during aging. Clinical research has developed analog tests, particularly based on virtual reality, which potentially enables a cross-discipline comparison of findings and the assessment of the efficiency of preclinical treatments in a more comparable setting. In the last section of the paper, the authors systematically evaluated if such would be the case, using data from ClinicalTrials.gov. The investigation focused on current enrolment criteria in age-associated cognitive decline clinical trials and whether sensitive behavioral tests are often used to enroll the elderly population suffering from age-related cognitive decline. They found that "pen and pencil" cognitive tests like Montreal Cognitive Assessment or Mini-Mental State Examination were predominantly used for enrolment criteria, lacking specificity to evaluate particular components of cognition affected in patients.

This raises possible recruitment bias as well as inconsistent approaches between preclinical and clinical research fields when

aiming to evaluate findings obtained in animal models among humans. Enrolment of older subjects screened using virtual-reality analog tests should be encouraged to detect milder/early forms of cognitive decline that might evade pen-and-pencil testing – the paradigms used to detect cognitive decline in rodents are particularly sensitive to spatial memories.

Altogether the authors provide an overview of altered brain activity during aging in humans and rodent models as well as strategies to diagnose age-related cognitive decline using a variety of tests. They discuss the interdisciplinary versatility of these methods and analyzed systematically their use for clinical trial enrolment.

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