Aging and the brain

Delivery Format: On Campus. Thursdays 3:00 - 4:30pm

GMS 7795 (1 credit)

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Graduate Assistant: None
Preferred Course Communications: Email

Course Description
This course will address questions of the primary causes of aging, and the history of research on aging. Theories of aging will be applied to the brain and cognitive decline and include biomarkers from biochemistry, to physiology, through to structural changes. Whenever possible, examples will be drawn from recent research in humans involving large populations and cellular molecular mechanisms examined using animal models. Differences in the rate of aging due to sex, resilience, compensation, and cognitive reserve, and the role of aging in disease will be discussed. Finally, therapeutic implications and related topics will be explored.

Course Objectives
After successfully completing this course, students will be able to:

• Identify the different theories/mechanisms/hallmarks of aging
• Describe early behavioral measures of cognitive decline in humans and animal models
• Exemplify measures of biological aging as they related to the brain
• Discuss sex differences and reserve/resilience mechanisms that may modulate the trajectory of age-related cognitive decline

OUTLINE

1. Introduction to aging, senescence, and longevity

   Causes and effects of increased longevity in humans
   Inflammation
   Lifespan, Healthspan, Gerospan
   Aging and diseases of aging

   Relationship of lifespan and cognitive decline
   Sex differences in lifespan, inflammation, cognitive aging, and dementia

   A chronological sequence of aging
A brief history of the rise in interest in to the molecular and cellular contributions to aging

Caloric restriction
Gene mutations in *C. elegans*.

2. Age-related cognitive decline and animal models

Cross-section versus longitudinal studies of cognition
Carryover and batch effects

Advantages of animal models (lifespan, genetic similarity, genetic mutation)

Concerns in choosing the correct animal model

How old is my mouse?

When does cognition decline?

Validity of animal models
Face validity
Construct validity
Predictive validity

Men, mice, mazes: choosing the appropriate task.

The hippocampus and episodic memory
Prefrontal cortex and executive function

3. Biological markers of aging across species

Characteristics of the perfect biomarker and the rate of aging.

Biological markers of aging and brain function, which can be applied across human and animal studies

- Measures of cognition (episodic memory or executive function)
- Blood (inflammation, exosomes, DNA methylation)
- Neuroimaging

Hallmarks of aging: The brain and everything else

4. Evolution theories of aging (DNA, RNA, epigenetics)

Evolution theories of aging

Mutation Accumulation Theory (Huntington’s, Parkinson’s, Alzheimer’s)

Antagonistic Pleiotropic Theory (Apoe, inflammation)

Genes for longevity/cognition interact with the environment

Somatic Mutation Theory

DNA repair epigenetics and the DNA methylation clock
5. Earliest markers of brain aging and predictors of cognitive decline

Cell senescence satisfies three criteria as biological markers of aging
  Function of cell senescence
  Markers of cell senescence during aging
  Inducing cellular senescence increases biomarkers of aging and functional decline
  Interventions that reduce cell senescence (senolytics)
  Senolytics and the brain

Inflammation and aging
  Markers of systemic inflammation
  Systemic inflammation and cognitive decline (COVID19)
  Neuroinflammation

6. Oxidative stress, calcium dysregulation, and senescent neurophysiology

Oxidative stress (Free Radical) theories of aging
  Sources of reactive oxygen species (ROS)
  Anti-oxidant enzymes
  Resilience to ROS damage in middle age

Updating the oxidative stress theory
  Reduces role for mitochondrial ROS
  Knockout or overexpression of antioxidant enzymes
  Sex and oxidative stress

Redox signaling and senescent neurophysiology
  \( \text{H}_2\text{O}_2 \) and disulfide bonds
  Growth of the afterhyperpolarization (AHP)
  Role for intracellular Ca\(^{2+} \) stores in regulating the AHP
  N-methyl-D-aspartate receptor (NMDAR) hypofunction
  NMDARs in episodic memory

7. Synaptic plasticity and the road to decreased synaptic connectivity prefrontal cortex

Long-term potentiation (LTP) and long-term depression (LTD)
  Ca\(^{2+} \)-dependent kinase/phosphatases and loss of synaptic connectivity

8. Prefrontal cortex

9. Mitochondrial dysfunction, Proteostasis and Autophagy

10. Treatments and therapies, class presentations

The student is expected to complete a short (minimum 5 single spaced pages, not including references) paper with an accompanied presentation on a topic not covered in detail in the course. The topic should include an examination of time course for biomarkers or treatment (i.e. when do differences emerge or when are treatments viable), relationship to cognition, human studies,
mechanisms and animals studies. Prior to starting the research, the student should discuss the topic with the instructor.

Possible examples include:

- Differential aging across brain regions: The cerebellum
- Role of astrocytes or oligodendrocytes in age-related cognitive decline
- Role of sleep in age-related cognitive decline

For drug treatments, any treatment approved by the instructor is acceptable; however, there are several sources students should search.

Intervention Testing Program to determine the effect of treatments on lifespan in mice.
https://www.nia.nih.gov/research/dab/interventions-testing-program-itp

Randomized clinical trials (RCT) are the gold standard for measuring the effectiveness of an intervention or treatment. The randomization of subjects to the treatment group and blinding the researchers to the treatment group reduces bias, increasing the confidence in the results. The effect of treatments on aging can be found at randomized clinical trials (https://www.clinicaltrials.gov/).

Examples of possible treatments: Rapomycin, non-steroidal anti-inflammatory drugs (NSAIDs), anti-oxidant drugs, Memantine, antihypertensive agents (e.g. captopril), stimulants, and specific lifestyle factors (keto or vegetarian diet, cognitive training using computer programs).

**Grading:** Satisfactory/Unsatisfactory. Grades will be determined based on class attendance, class participation, and a final paper/presentation.

**Exam Policy: No exam**

**Policy Related to Required Class Attendance:**
Requirements for class attendance and, assignments, and other work in this course are consistent with university policies that can be found at:
https://catalog.ufl.edu/ugrad/current/regulations/info/attendance.aspx

Excused absences must be consistent with university policies in the Graduate Catalog (http://gradcatalog.ufl.edu/content.php?catoid=10&navoid=2020#attendance). Additional information can be found here:
https://catalog.ufl.edu/ugrad/current/regulations/info/attendance.aspx

**Academic Integrity:**
Students are expected to act in accordance with the University of Florida policy on academic integrity. As a student at the University of Florida, you have committed yourself to uphold the Honor Code, which includes the following pledge:

“We, the members of the University of Florida community, pledge to hold ourselves and our peers to the highest standards of honesty and integrity.”

You are expected to exhibit behavior consistent with this commitment to the UF academic community, and on all work submitted for credit at the University of Florida, the following pledge is either required or implied:

“On my honor, I have neither given nor received unauthorized aid in doing this assignment.”

It is your individual responsibility to know and comply with all university policies and procedures regarding academic integrity and the Student Honor Code. Violations of the Honor Code at the University of Florida will not be tolerated. Violations will be reported to the Dean of Students Office for consideration of disciplinary action. For additional information regarding Academic Integrity, please see Student Conduct and Honor Code or the Graduate Student Website for additional details:

https://www.dso.ufl.edu/sccr/process/student-conduct-honor-code/
http://gradschool.ufl.edu/students/introduction.html

Please remember cheating, lying, misrepresentation, or plagiarism in any form is unacceptable and inexcusable behavior.

Online Faculty Course Evaluation Process:
Students are expected to provide professional and respectful feedback on the quality of instruction in this course by completing course evaluations online via GatorEvals. Guidance on how to give feedback in a professional and respectful manner is available at https://gatorevals.aa.ufl.edu/students/. Students will be notified when the evaluation period opens, and can complete evaluations through the email they receive from GatorEvals, in their Canvas course menu under GatorEvals, or via https://ufl.bluera.com/ufl/. Summaries of course evaluation results are available to students at https://gatorevals.aa.ufl.edu/public-results/.

Support Services:
Accommodations for Students with Disabilities:
Students with disabilities who experience learning barriers and would like to request academic accommodations should connect with the Disability Resource Center by visiting https://disability.ufl.edu/students/get-started/. It is important for students to share their accommodation letter with their instructor and discuss their access needs, as early as possible in the semester. The College is committed to providing reasonable accommodations to assist students in their coursework. Counseling and Student Health: Students sometimes experience stress from academic expectations and/or personal and interpersonal issues that may interfere with their academic performance. If you find yourself facing issues that have the potential to or
are already negatively affecting your coursework, you are encouraged to talk with an instructor and/or seek help through University resources available to you.

- The Counseling and Wellness Center 352-392-1575 offers a variety of support services such as psychological assessment and intervention and assistance for math and test anxiety. Visit their web site for more information: http://www.counseling.ufl.edu. 5 On line and in person assistance is available.

- You Matter We Care website: http://www.umatter.ufl.edu/. If you are feeling overwhelmed or stressed, you can reach out for help through the You Matter We Care website, which is staffed by Dean of Students and Counseling Center personnel.

- The Student Health Care Center at UF Health is a satellite clinic of the main Student Health Care Center located on Fletcher Drive on campus. Student Health at UF Health offers a variety of clinical services. The clinic is located on the second floor of the Dental Tower in the Health Science Center. For more information, contact the clinic at 392-0627 or check out the web site at: https://shcc.ufl.edu/

- UF Health Emergency Room / Trauma Center: For immediate medical care call 352-733- 0111 or go to the emergency room at 1515 SW Archer Road, Gainesville, FL 32698, ufhealth.org/emergency-room-trauma-center.

- University Police Department: Visit police.ufl.edu/ or call 352-392-1111 (or 9-1-1 for emergencies).

- Crisis intervention is always available 24/7 from: Alachua County Crisis Center: (352) 264-6789 http://www.alachuacounty.us/DEPTS/CSS/CRISISCENTER/Pages/CrisisCenter.aspx

Do not wait until you reach a crisis to come in and talk with us. We have helped many students through stressful situations impacting their academic performance. You are not alone so do not be afraid to ask for assistance.

**Academic Resources**

**E-learning technical support:** Contact the UF Computing Help Desk at 352-392-4357 or via email at helpdesk@ufl.edu.

**Career Connections Center:** Reitz Union Suite 1300, 352-392-1601. Career assistance and counseling services career.ufl.edu/.

**Library Support:** cms.uflib.ufl.edu/ ask various ways to receive assistance with respect to using the libraries or finding resources.
**Teaching Center:** Broward Hall 352-392-2010 or to make an appointment 352 392-6420. General study skills and tutoring. [teachingcenter.ufl.edu](http://teachingcenter.ufl.edu/).

**Writing Studio:** 2215 Turlington Hall, 352-846-1138. Help brainstorming, formatting, and writing papers. [writing.ufl.edu/writing-studio/](http://writing.ufl.edu/writing-studio/)

**Student Complaints On-Campus:** [sccr.dso.ufl.edu/policies/student-honor-code-studentconduct-code/](http://sccr.dso.ufl.edu/policies/student-honor-code-studentconduct-code/)

On-Line Students Complaints: distance.ufl.edu/student-complaint-process