Lecture Overview

- Global costs & impact of Neurodegenerative Diseases

- Alzheimer’s Disease (AD)
  - Symptoms, Pathology, Cellular Mechanisms

- Parkinson’s Disease (PD)
  - Symptoms, Pathology, Cellular Mechanisms

- Traumatic Brain Injury (TBI)
  - Symptoms, Pathology, Cellular Mechanisms

- Investigating neurodegenerative diseases in Fruit Flies at Lehigh
Leading Causes of Death in the U.S.

1. Heart Disease
2. Cancer
3. Chronic lower respiratory diseases
4. Unintentional injuries
5. Cerebrovascular diseases
6. Alzheimer’s Disease
7. Diabetes mellitus
8. Influenza & pneumonia
9. Nephritis
10. Suicide

Alzheimer’s disease is the sixth leading cause of death in the United States and the fifth leading cause among the elderly.

It’s the only cause of death in the top 10 in America that CANNOT BE PREVENTED, CURED, OR SLOWED.
Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2014

![Bar Chart]

- Breast cancer: -1%
- Prostate cancer: -9%
- Heart disease: -14%
- Stroke: -21%
- HIV: -54%
- Alzheimer's disease: 89%

Created from data from the National Center for Health Statistics.208, 219
5.3 million Americans diagnosed with Alzheimer’s disease

1 in 9 individuals over the age of 65
1 in 3 individuals over the age of 85

Worldwide: 1 every 6 seconds
All dementia: 1 every 3 seconds
The total estimated worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to US$ 2 trillion by 2030.

If global dementia care were a country, it would be the 17th largest economy in the world exceeding the market values of companies such as Apple and Google.

This is only for caring for patients:

- Not for treatments
- Not for cures
- Not for drug discovery
- Not for research
What is the biggest risk factor for most neurodegenerative diseases? (Alzheimer’s, Parkinson’s, etc...)

Exceptions:
Amyotrophic Lateral Sclerosis (ALS)
Huntington’s Disease (HD)

Average Age of Onset
Alzheimer’s Disease = ~ 65+ years
Parkinson’s Disease = ~ 63 years

“early onset” in 30’s or 40’s
Our aging population

1) Increased life expectancy

![Life Expectancy in Developed Countries: 1840-2009](image)

Source: National Institute on Aging

2) Older individuals make up a larger percentage of the global population

![Young Children and Older People as a Percentage of Global Population: 1950-2050](image)

Incidence rate for most neurodegenerative diseases increases with age

Baby Boomers
Born between 1946 and 1964
In 2019: Currently age 55-73
## Symptoms of Alzheimer’s Disease (AD)

AD is the most common form of dementia

### Cognitive Impairment
- Confusion
- Memory deficits
  - (1) Trouble forming new memories
  - (2) Long-term memories affected later
  - (3) Childhood memories are among the last to be lost

### Behavioral Changes
- Irritability
- Personality changes
- Wandering ➔ Getting lost

### Psychological Issues
- Loneliness
- Depression

[www.alzdiscovery.org](http://www.alzdiscovery.org)
Pathology of Alzheimer’s Disease

Healthy

- Cerebral cortex: Responsible for language and information processing
- Hippocampus: Critical to the formation of new memories

Alzheimer’s Disease

- The cortex shrivels up, damaging areas involved in thinking, planning and remembering
- Ventricles filled with cerebrospinal fluid grow larger
- Hippocampus shrinks severely

Plaques

- Amyloid-β

Tangles

- Tau

Source: Alzheimer’s Association
The region of the brain that is primarily damaged by Alzheimer’s Disease is called the **hippocampus**.

**Hippocampus** means “seahorse” in Greek.

The Hippocampus is required for the **formation** of new memories, and **consolidation** into long-term memories.
The Role of Amyloid-β in Alzheimer’s Disease

Normal cleavage product = Aβ-40 (soluble)

Abnormal cleavage product = Aβ-42 (insoluble) → Aggregates → Plaques
The Role of Tau in Alzheimer’s Disease

Tau loses the ability to stabilize microtubules, and gains a “sticky” property that results in the formation of tangles.
Protein aggregates can spread throughout the nervous system

Misfolded proteins that stick together to form aggregates can induce normal proteins nearby to mis-fold as well.

Proteins can break off from aggregates and start these events over again in a process called **Seeding**.

These aggregates can then **spread** between neurons and throughout the brain

*Jucker & Walker, 2013*
Parkinson’s Disease (PD) is the 2nd most prevalent neurodegenerative disease. Parkinson’s Disease is the most prevalent movement disorder. Currently ~1 million Americans Diagnosed with PD.
Clinical symptoms of Parkinson’s Disease

Locomotor Impairment

- Difficulty moving when you want to
- Uncontrolled movement when you don’t want to
- Bradykinesia - slow movement
Loss of Dopaminergic neurons in the **substantia nigra** causes defects in motor coordination.
The protein most closely associated with PD is called **α-Synuclein**.

α-Synuclein localizes to synaptic terminals.

1) Recycling of synaptic vesicles

2) Trafficking of synaptic vesicles from reserve pool to readily releasable pool
Point mutations in α-Synuclein make the protein more prone to aggregation.

Too much α-Synuclein (extra copies) also result in aggregation.
Aggregates of α-Synuclein block lysosomal degradation

**Autophagy** = “self eating”

Breaking down and recycling cellular material (proteins, organelles, etc.)
Traumatic Brain Injury (TBI)

Broad term referring to any injury impacting the brain

Chronic Traumatic Encephalopathy (CTE)

Clinical Diagnosis
Accumulation of Tau pathology in the Brain

Case 1
- Alzheimer’s Disease
- Age: 85

Case 2
- Chronic Traumatic Encephalopathy (CTE)
- Age: 40’s

Mckee et al., 2013
The History of CTE

Dementia Pugilistica
“Punch-drunk” (1928)

“Daze or confusion after repeated blows to the head”
The History of CTE

Mike Webster (1952 – 2002)
4 Super Bowl Championships
Amnesia
Dementia
Depression
Died from heart attack at age 50

Dr. Bennet Omalu
Performed autopsy on Mike Webster
Found Widespread deposits of Tau throughout the brain.
Estimated that Mike Webster sustained 70,000 blows to the head over his career.
First diagnosis of CTE in an NFL player.
The History of CTE

Mike Webster

Terry Long

Justin Strzelczyk

Tom McHale
Growing prevalence of CTE

Boston University: As of September 2015, **87 of 91** deceased former NFL players tested positive for CTE

"Every case of diagnosed CTE has had one thing in common: a history of repetitive hits to the head."

— Robert Stern, director of clinical research for Boston University’s CTE center
2017 Study Evaluates CTE in football players at different levels

JAMA | Original Investigation

Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football

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CTE diagnosis

High School: 21%
College: 91%
NFL: 110 of 111 (99%)
Humans typically receive concussions with a “g-force” of ~80 – 100 g’s

Players at the University of Oklahoma had Head Impact Telemetry Systems added to their helmets to measure collisions.

Players frequently had collisions measuring over 98 g’s (The approximate force of a sledgehammer)
Damage to the brain in a closed head injury

The brain is not stationary inside the skull.

It is bathed in Cerebral Spinal Fluid (CSF)

The brain can be damaged from impact, but also from acceleration or deceleration secondary to the force of impact.
The force from the impact causes the brain to hit the inner surface of the skull and rebound against the opposite side.

Padding on the outside of the head can only do so much. Helmets have been very effective at preventing skull fractures, but not concussions and other types of closed head injuries.
When the brain moves around inside the skull after impact, the tissue can stretch and tear.

1) Neuronal loss

2) Release of toxic proteins
Many sources of traumatic brain injury

Over 115,000 troops have suffered traumatic brain injury over the last 10 years.
Current Treatments for TBI

• Current focus on monitoring individuals after injury
  • Avoiding repetitive injuries

• Identify biomarkers
  • Read-out in living patients to study pathology
  • Current diagnosis is in autopsy

• Why are neurofibrillary tangles (tau aggregates) widespread in cases of CTE?
  • Will any treatments to clear these tangles help with CTE?
  • “You pop a pill before you play, a medicine that prevents the buildup of tau. Like you take an aspirin to prevent heart disease.” - Bennet Omalu
Modeling Neurodegenerative Diseases in *Drosophila*

Babcock Lab
Seeding and spreading of aggregates

Misfolded proteins that stick together to form aggregates can induce normal proteins nearby to misfold as well.

Proteins can break off from aggregates and start these events over again in a process called Seeding.

These aggregates can then spread between neurons and throughout the brain.
Investigating neurodegenerative diseases in *Drosophila*

- Identify genes involved in a specific process
- Test the function of genes of interest

Drosophila models of neurodegenerative diseases

- Alzheimer’s Disease: Tau, Amyloid-β
- Parkinson’s Disease: α-Synuclein
- Huntington’s Disease: Huntingtin

C17-Gal4, UAS-GFP

Express proteins implicated in human Neurodegenerative Diseases

- Mutagenesis screens (traditional and modifier)
- RNAi
- Genome editing
- Transgenesis

Forward genetics

Reverse genetics

* Drosophila models of neurodegenerative diseases
Manipulating subsets of neurons in the *Drosophila* nervous system

Olfactory Receptor Neurons
*Or83b-Gal4*

UAS-mRFP-HttQ138

*Or83b-Gal4 > UAS-GFP*

*Weiss et al., 2012*
Huntingtin aggregates spread beyond ORN terminals

or83b-Gal4 > UAS-GFP + UAS-htt.RFP

D6

GFP

Htt.RFP

D30

GFP

Htt.RFP
Huntingtin aggregates spread beyond ORN terminals

Or83b-Gal4 > UAS-GFP  UAS-htt.138Q.mRFP
Huntingtin aggregates spread beyond ORN terminals
1. Aging is the biggest risk factor for Alzheimer’s & Parkinson’s Disease.

2. Particular areas of the brain are vulnerable in each disease.
   - The symptoms reflect the functions of those brain areas
     (Hippocampus (AD) & Substantia Nigra (PD))

3. Key Players in these diseases:
   - (AD) Tau, Amyloid-Beta
   - (PD) α-Synuclein

4. The relationship between the brain and the skull is large part of why the brain is susceptible to injury after impact.