Outline

- Global costs & impact
- 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 University
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

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Percentage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>-1%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>-9%</td>
</tr>
<tr>
<td>Heart disease</td>
<td>-14%</td>
</tr>
<tr>
<td>Stroke</td>
<td>-21%</td>
</tr>
<tr>
<td>HIV</td>
<td>-54%</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>89%</td>
</tr>
</tbody>
</table>

Created from data from the National Center for Health Statistics.201,21
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 Global Cost of Alzheimer’s Disease & Dementia

GDP ($ Billions)
- Mexico ------------ 1,082
- Indonesia -------- 936
- Netherlands ----- 762
- Turkey ----------- 751
- Switzerland ------ 651

This money is only for **caring for patients:**

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

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

**AGE**

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

“early onset” in 30’s or 40’s
Aging population

1) Increased life expectancy

2) Older individuals make up larger percentage of global population

Source: National Institute on Aging
Incidence rate for most neurodegenerative diseases increases with age

**Baby Boomers**

Born between 1946 and 1964

In 2018: Currently age 54-72
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
  • Loneliness
  • Depression

www.alzdiscovery.org
Alzheimer’s disease

Healthy brain

Cerebral cortex:
Responsible for language and information processing

Alzheimer’s disease brain

The cortex shrivels up, damaging areas involved in thinking, planning and remembering

Ventricles filled with cerebrospinal fluid grow larger

Hippocampus:
Critical to the formation of new memories

Hippocampus shrinks severely

Plaques

Neurofibrillary Tangles

Amyloid-β

Source: Alzheimer’s Association
The hippocampus

“seahorse” in Greek

Involved in the **formation** of new memories, and **consolidation** into long-term memories
Role of Amyloid-β in Alzheimer’s Disease

Normal cleavage product = Aβ-40 (soluble)
Abnormal cleavage product = Aβ-42 (insoluble) → Aggregates → Plaques

http://jonlieffmd.com
Role of Tau in Alzheimer’s Disease

- **Tau** (microtubule-associated protein)
- Hyper-phosphorylation of Tau
- Destabilized microtubules (impaired axonal transport)
- Neurofibrillary Tangles
- Paired helical filaments
- Hyperphosphorylated tau proteins

(Querfurth & LaFerla, 2010)
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.
Parkinson’s Disease
Clinical symptoms of Parkinson’s Disease

**Locomotor Impairment**

- **Difficulty moving when you want to**
- **Uncontrolled movement when you don’t want to**

2<sup>nd</sup> most common neurodegenerative disease (~ 1 million Americans currently diagnosed)
Loss of Dopaminergic neurons in the substantia nigra causes defects in motor coordination.
Alpha-synuclein localizes to synaptic terminals

1) Recycling of synaptic vesicles

2) Trafficking of synaptic vesicles from reserve pool to readily releasable pool
Aggregates of alpha-Synuclein are the primary component of Lewy Bodies

- **Point mutations** in alpha-synuclein make the protein more prone to aggregation
- Too much alpha-synuclein (extra copies) also result in aggregation
Aggregates of alpha-synuclein block lysosomal degradation

**Autophagy** = “self eating”
Breaking down and recycling cellular material (proteins, organelles, etc....)
Traumatic Brain Injury (TBI)

Chronic Traumatic Encephalopathy (CTE)

Stage I CTE
Stage II CTE
Stage III CTE
Stage IV CTE
Comparison of Tau pathology

**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

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.

**Bathed in CerebroSpinal Fluid (CSF)**

Brain can be damaged from impact, but also from acceleration or deceleration secondary to the force of impact.
Damage to the brain in a closed head injury

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.
Diffuse Axonal Injury

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.
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.

*Jucker & Walker, 2013*
Investigating neurodegenerative diseases in *Drosophila*

Identify genes involved in a specific process

Test the function of genes of interest

Drosophila models of neurodegenerative diseases

Express proteins implicated in human Neurodegenerative Diseases

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

C17-Gal4, UAS-GFP
Manipulating subsets of neurons in the *Drosophila* nervous system

*Or83b-Gal4* > *UAS-GFP*

*Or83b-Gal4*

*UAS-mRFP-HttQ138*

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
Summary

1. Aging is the biggest risk factor for diseases like 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 & Substantia Nigra)

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

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