WHY DOING CROSSWORDS IS NOT HELPING YOU PREVENT ALZHEIMER’S DISEASE

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Overview

Part I: Understanding Alzheimer Disease
- Normal aging VS dementia
- Alzheimer's disease
  - Intro, symptoms, progression and treatment
- What goes on in the brain in AD?
  - Pathology of the disease

Part II: Risks and Prevention: A Balancing Act
- Risk factors (cumulative, tipping the scale)
- Cognitive reserve
  - The nun study
- How to best protect your brain
PART I: UNDERSTANDING ALZHEIMER DISEASE
Dementia

- Dementia refers to a set of symptoms that are caused by disorders that affect the brain.
- Symptoms may include memory loss, problems with thinking and problem-solving, and language problems.
- Changes in mood or behaviour are also common.
- Impairments in these processes are severe enough to affect daily life.
- Dementia is progressive (symptoms worsen as more brain cells die).
- Dementia is not a specific disease; many diseases cause dementia (e.g. Alzheimer disease, Huntington’s disease, head trauma, Parkinson’s disease, etc.)
Normal Aging VS Dementia

- Memory loss is associated with normal aging; however, these problems are caused by *dysfunctional neurons* rather than *dying neurons*.
  - This represents the main difference in neuronal pathology between normal aging and dementia.
- While both normal aging and dementia target neurons in the hippocampus, different patterns of anatomical dysfunction are observed (different cell populations are affected; Small et al., 2011).
- Almost 40% of people over the age of 65 experience some form of memory loss — this is known as ‘age-associated memory impairment’, has no underlying medical cause, and is considered a normal part of the aging process.
Normal Aging VS Dementia

- Age-associated memory impairment is not the same as Alzheimer disease and other forms of dementia
- Some ways to distinguish the two based on functional abilities

<table>
<thead>
<tr>
<th>Normal Aging</th>
<th>Dementia</th>
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<tbody>
<tr>
<td>Forgetting details of a conversation or an event that took place last year</td>
<td>Failure to recall details of recent events or conversations</td>
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<td>Forgetting names of acquaintances</td>
<td>Not recognizing or knowing good friends and family members</td>
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<tr>
<td>Occasionally having a difficult time finding words</td>
<td>Frequently pauses and word substitutions during a conversation</td>
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<tr>
<td>Individual worries about memory loss, but family members do not</td>
<td>Family worries about memory loss, but individual is not aware of any problems</td>
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Alzheimer Disease

- First described by Dr. Alois Alzheimer in 1906
  - He followed a patient in an asylum with symptoms including **memory loss, language problems, and unpredictable behaviour**
  - After her death, Alzheimer noticed abnormal clumps and tangled fibers in her brain
  - By 1911, doctors were using Alzheimer’s research to base diagnoses – but abnormal protein forming aggregates not identified until 1990s
AD: The Stats

- AD is the leading cause of dementia
  - Accounts for 60-80% of cases
- It is a neurodegenerative disease, following a specific pattern of degeneration
- Globally, number of people suffering from dementia estimated around 25 million, and expected to double by 2040
- Of the top 10 leading causes of death in the US, AD is the **only disease** that cannot be prevented, slowed, or cured
AD: Symptoms

◦ **Mild cognitive impairment (MCI)**
  ◦ Refers to memory problems greater than expected for age, but no daily functional impairments observed
    ◦ Older people with MCI at greater risk for developing AD, **but not all do**
  ◦ AD progresses in stages – mild, moderate and severe
    ◦ Memory problems usually appear first, but symptoms vary between individuals
    ◦ For many, non-memory aspect of cognition are affected first
      ◦ E.g. word finding, vision/spatial issues, impaired reasoning or judgment
AD: Symptoms

- **Mild AD**: Increasing memory loss, other cognitive difficulties
  - Wandering/getting lost, trouble handling money, repeating questions, taking longer to complete tasks, personality and behavioural changes
  - Apathy, depression

- **Moderate AD**: Involvement of language, reasoning, sensory processing, and conscious thought
  - Memory problems worsen, trouble recognizing friends and family
  - Unable to learn new things, difficulty with multi-step tasks (e.g. getting dressed), or coping with new situations
  - At this stage, people may have hallucinations, delusions and paranoia, and may behave impulsively

- **Severe AD**: Massive cell loss leads to dependence
  - Cannot communicate, bed ridden as body shuts down
AD: Symptoms

- Summary of symptoms clustered by category (all are progressive during course of disease)
  - **Cognitive and Functional abilities**
    - Changes in ability to understand, think, remember and communicate
  - **Emotions and Mood**
    - Increased apathy/depressive symptoms (e.g. anhedonia), decreased expression of emotions, withdrawal from social circles/family
  - **Behaviour**
    - Increase in ‘out of character’ behaviours (e.g. hiding possessions, physical outbursts, restlessness, repeating things)
  - **Physical Abilities**
    - Impairments in coordination and mobility influence individual’s ability to perform daily tasks independently (e.g. eating, bathing, dressing)
AD: What Causes it?

◦ Most of the time, cause is not known (called sporadic or late onset, 90-95% of cases); sometimes, familial link (called early-onset, 5-10% of cases)
  ◦ Late onset – diagnosis after 65
  ◦ Early onset – diagnosis before 65
◦ Familial – some genes have been linked to AD
  ◦ E.g. trisomy 21; Down syndrome
AD: What Causes it?

- **Sporadic** — cause unknown, likely a combo of genetic and environmental risk factors
- Age = biggest risk factor
- Affects 1% of ppl >65; 50% of ppl >85
AD: What Causes it?

- Gene: There are 3 types of the apolipoprotein E (APOE) gene (e2, e3, and e4)
  - APOE is a protein that helps break down amyloid-beta (Aβ), a major component of the plaques seen in AD
  - The e3 version is most common (>50% population has this version)
  - e4 allele seems to be less effective than e2 version at breaking down Aβ
  - Inheriting 1 e4 allele ↑ risk of developing AD
  - Inheriting 2 e4 alleles ↑ risk even more
AD Pathology

- AD can only be **definitively diagnosed** after death, when patterns of brain damage can be clinically assessed within the context of symptoms patient exhibited.
- Neuronal death begins in structures important for memory and emotion (e.g. the hippocampus), and spreads to the cortex (outermost layers of brain) over time.
- Brain atrophies (shrinks from cell death), and loss of tissue leads to narrower gyri, wider sulci, and enlarged ventricles.
AD Pathology

- Two key pathological features of AD:
  - Beta-amyloid plaques (form outside cells)
  - Neurofibrillary tangles (form inside cells)

- Beta-amyloid plaques can elicit an immune response by glial cells, and can deposit near blood vessels – weakens blood vessel wall and increases risk of hemorrhage (rupture of vessel wall)

- Tangles lead to dysfunctional axons, and cells initiate apoptosis

(A: Astrogliosis in hippo neurons
B: Aβ deposits near blood vessels

(Verkhratsky et al., 2010)
AD Pathology

- **Importance of GLIAL CELLS**
- **Beta-amyloid (Aβ)** builds up in the synapse – the place two neurons communicate
- **Microglia** and **astrocytes** – two types of regulatory cells in the brain
  - Once thought to be ‘supporting cells’ only – we now know they play ACTIVE roles in the health and disease of brain cells.
  - Roles in communication, inflammation and disease, immune response
- **Microglia** normally clean up excess Aβ protein that builds up in the **synapse** (‘debris clearing’ aka janitorial role)
  - However, microglia are also activated by excessive plaques
  - They release pro-inflammatory cytokines – causing damage to nearby cells – can even remove synapses (via phagocytosis)
AD Pathology

- **Astrocytes**
  - Also involved in janitorial tasks (e.g. clearing Aβ)
  - **Important**: astrocytes and microglia talk to each other, which is a factor in how they respond to cellular stress
  - Astrocytes become activated later in the disease and add to the inflammatory response
  - **Activated (or reactive) astrocytes** have been observed in the brains of patients with AD (Perez-Nievas & Serrano-Pozo, 2018)
  - Mouse study (image on the right) – shows loss of branching in astrocytes (B) compared to control animals (A) in the hippocampus

(Verkhratsky et al., 2010)
Treatment

◦ None of currently available pharmacological treatments slow or stop damage to neurons

◦ Six drugs for AD are FDA approved, and temporarily improve symptoms by increasing NTs in the brain - effectiveness of drugs varies person to person

◦ Between 2002-2012, 244 drugs for AD were tested in clinical trials
  ◦ Only 1 successfully completed clinical trials and became FDA approved

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Treatment

- Developing effective treatments for AD is challenging for a number of reasons:
  - Cost of drug development
  - Time required to observe slowing/changing of disease course in response to treatment
  - Blood brain barrier – getting the drug to the brain

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So...

- Is there any GOOD news?
- YES
- We will get to that after the break 😊
PART II: RISKS AND PREVENTION: A BALANCING ACT
Is AD our brain’s destiny?

- We all hope to live until old age… but what does that mean for our brains?
- Based on what we have already learned, the reward of living until 85 is a 50% of AD
  - Don’t think it will be you?
- One reason Alzheimer’s creates so much fear – feeling of helplessness to stop it
  - Is this true, though?
  - Has research given us any hints into how we might protect our brains from AD?
The Synapse and AD

◦ In Part I, we discussed the importance of the synapse (where the amyloid plaques are building up)

◦ The synapse is important because it is where chemical communication takes place
  ◦ We think, feel, hear, and remember here

◦ We also discussed the importance of the microglia (i.e. janitor cells) that clear away accumulated protein/debris in cells

◦ Microglia clear amyloid-beta from the synapse, but why is it in the synapse at all?
Amyloid-beta build-up

- Amyloid-beta typically released by neurons and can interact with neurons and glial cells
- Important cellular function in the healthy brain, including recovery from injury, communication, and protection from infection – this type of amyloid-beta is protective
- Problems arise when improperly cut protein starts sticking together and forms oligomers, then plaques
Tipping Point

- Molecular causes of AD under debate, but many believe **pathology** begins when **amyloid-beta** begins to accumulate in the synapse
- Too much released, not enough cleared, or both – starts to get sticky
- Build-up begins in our 40s, but if tipping point is reached, we are symptomatic
- Pre-tipping point memory problems are different from post-tipping point memory problems
Tipping Point

- **PRE-tipping point:**
  - Why did I come into this room?
  - Where did I leave my keys?
  - What is that LinR lecturer’s name again?
  - These are normal types of forgetting (and in fact, may have nothing to do with memory)

- **POST-tipping point:**
  - Finding keys in microwave
  - Finding keys and thinking ‘what are these for?’
Tipping Point Reached

- Microglia are hyperactivated and releasing substances to sound the alarm
  - May even remove the synapse if cells under too much stress
- Tau tangles forming in neurons are choking them off from the inside
- So by mid-stage AD, we have:
  - Extensive inflammatory processes and removal of synapses coordinated by glial cells
  - Cell damage and death (tau tangles, dying neurons)
- YIKES – can we stop this disease?
Preventing Tipping?

- Many scientists focus on preventing build-up of plaques to treat AD
- Prevent the war on synapses by prevent the accumulation of amyloid-beta (meaning the eventual cure will be a preventative drug)
- Recent paper (Shea et al., 2019) developed a synthetic protein that stuck to oligomers and prevented aggregation (tested in cells and animals)
- Even newer research published only a few weeks ago (Ewers et al., 2019) identified a correlation between a protein released by microglia and cognitive decline in over 300 patients with AD (more of this protein led to slower cognitive decline)
- But how can we prevent the tipping point from being reached? Is there anything we have do?
Preventative Drug @ 40?

○ Would need to take drug years before symptoms appear

○ Possible this is why previous clinical trials have failed
  ○ If individuals are already symptomatic, too late to prevent Aβ buildup
  ○ If treatment is attempting to break up oligomers, no use blowing out the match once the forest is ablaze

○ BUT there is good news if we are not yet symptomatic – turns out our lifestyle can influence how Aβ accumulates
  ○ This means there are things we can do to prevent the scales from tipping
Tipping the Scales

• Think of it as a balance, with risk factors on one side and preventative factors on the other

• If the scale hits the ground, you become symptomatic (develop the disease)

• But how many factors are in your control to hopefully prevent the development of AD?
Tipping the Scales

**RISKS**
- AGE (e.g. 50-55)
  - You’ve accumulated some plaques with age
- DNA
  - Some genes alone are enough
  - Most increase risk only APOE4

**PREVENTATIVE**

**SLEEP**
- Power cleanse for the brain
- Microglia, toxins in CSF
- One night of poor sleep ↑ Aβ
  - ↑ Aβ leads to poor sleep - cycle

**CARDIOVASCULAR HEALTH**
- Obesity, smoking, high BP/cholesterol, diabetes all ↑ risk of AD

Can’t change our age or our genes… so what can we do?

**SO** – heart-healthy Mediterranean diet and aerobic exercise, 7-8 hours of sleep
What if you haven’t done any of this?

**YOU**

- In your 60s…
  - Haven’t taken good care of body/brain through diet
  - Have a couple of genes that increase your risk of AD
  - Ran yourself silly for years (poor sleep hygiene)

NOW are you doomed to get AD? Maybe not!
The Nun Study

- **Ideal group for studying risk factors of dementia – why?**
  - Relatively homogenous group with similar lifestyle – typically huge challenge of human research
  - Started in the 1980s and is ongoing – more than 700 nuns donated bodies and brains to science in the United States
  - In this group, none smoked, none drank excessively, none had partners and each lived a fairly routine, meaningful life
  - At autopsy, several of the nuns’ brains showed all physical characteristics of an Alzheimer’s diseased brain – yet interestingly, none were symptomatic while alive
What can we learn from the nun study?

- **COGNITIVE RESERVE**
  - Many nuns remain involved in education and service well into old age
  - What is cognitive reserve?
  - Let’s say you only know one thing about me – I’m a neuroscientist
  - Lose this connection – lose all memory of me
  - Let’s say you know a few things about me, though…
  - Individuals with more education have lower risk of developing AD – likely due to greater *cognitive reserve*
So what can we do?

- Activities that create and strengthen new neural connections based on principles of neuroplasticity
  - Behaviours we engage in frequently are like ruts in a road – easier to travel
  - Learning **new things** carves out new pathways (i.e. creates new neural connections) which can be strengthened through **practice**

- **SO:** why aren’t crosswords helpful in the quest to prevent AD?

- **We need to engage in activities which are NEW to our brains**
  - Recall task – retrieval of information already there
  - Good news = you’re getting better at doing crosswords! 😊
So what can we do?

- We need to engage in activities which spark the creation of new neural pathways
  - Learn new things
  - Build cognitive reserve
- We need to prioritize heart health
- We need to be protectors of our sleep
- What kinds of ‘new’ things?
  - Examples are endless since new to you may be different than new for someone else!
  - Learn a language, read, cook different foods using recipes, learn a new hobby/craft, dance
  - Go to Learning in Retirement lectures =
Coping with Memory Loss

- Some tips to help cope with memory loss:
  - Keep a routine
  - Organize information (post-its/notes, calendars, reminders for pills/appointments)
  - Put items in safe/same spot (i.e. car keys, phone, wallet)
  - Repeat information when it is learned (e.g. names), and use associations to help recall
  - Tell stories to others

- When interacting with someone with any form of memory loss, remember to be patient, seek support/community, and remember that your own health (both physical and mental) is required to be in a good state for you to care for another

“Alzheimer’s creates a kind of friction that the family needs to be strong for. You have to hold onto things and know what is true in life.” - Candy Crowley
Thank you!