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Metabolic Dysfunction, Oxidative Stress, and Neuroinflammation in the Down Syndrome Basal Forebrain at Birth

By

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Chapter 1: The Wisconsin Initiative for Science Literacy – Vulnerability of Neurons in Down syndrome Contributes to Alzheimer's disease and Memory Impairment

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The Wisconsin Initiative for Science Literacy

I am excited about the work that I do, but I know my research alone won't change the world. It is a small piece of a much larger puzzle. But my little piece combined with pieces of research from other scientists could one day improve human health. It may not be today or tomorrow, but one day all the pieces could come together to inform a new treatment for disease. I strongly believe that I, along with other scientists, have an obligation to make our research accessible to everyone. Everyone – the people who may one day receive these treatments, the taxpayers funding the research, the agencies providing the grant money – should be able to understand the research we are doing.

The best advice I received from my undergraduate mentor was to explain my work so that my grandma could understand it, so that is what I am going to do in this chapter. I would like to thank Professor Bassam Shakhashiri for his dedication to making science fun and accessible. Professor Shakhashiri started the Wisconsin Initiative for Science Literacy program which provides a platform for and encourages PhD students to communicate their science to the public. I would like to thank my editor, Elizabeth Reynolds, and program coordinator, Cayce Osborne, for their feedback, encouragement, and support throughout this process. And now, in a few short pages, I am going to tell you what I worked on for the last five years in my PhD.

Alzheimer's disease

In November 1901, a 51-year-old woman was admitted to the Frankfurt Psychiatric Hospital for worsening paranoia, sleep problems, memory loss, and confusion. She was observed by clinical psychologist and neuroanatomist, Dr. Alois Alzheimer, until her death

5 years later. Following the woman's death, Dr. Alzheimer examined her brain and noticed abnormal protein aggregates that are known today to be neurofibrillary tangles and amyloid plaques. Dr. Alzheimer presented this case in 1906 at a conference for psychiatrists, and in 1910, this disease was coined Alzheimer's disease[1].

Today, it is estimated that 24 million people worldwide are living with Alzheimer's disease. Alzheimer's disease affects approximately 1 in 10 people over the age of 65. By 85 years old, around 1 in 3 people suffer from the disease. Symptoms of Alzheimer's disease include the progressive worsening of memory, reasoning, language, spatial understanding, and behavioral changes such as agitation, mood swings, and paranoia[2].

Causes of Alzheimer's disease

Alzheimer's disease in the general population is classified into two forms, familial and sporadic. Around 5% of Alzheimer's disease cases are familial Alzheimer's disease (fAD) and about 95% of cases are sporadic Alzheimer's disease (sAD) (Figure 1). Although both forms of Alzheimer's disease lead to similar symptoms and protein aggregates in the brain, they differ in how the disease develops.

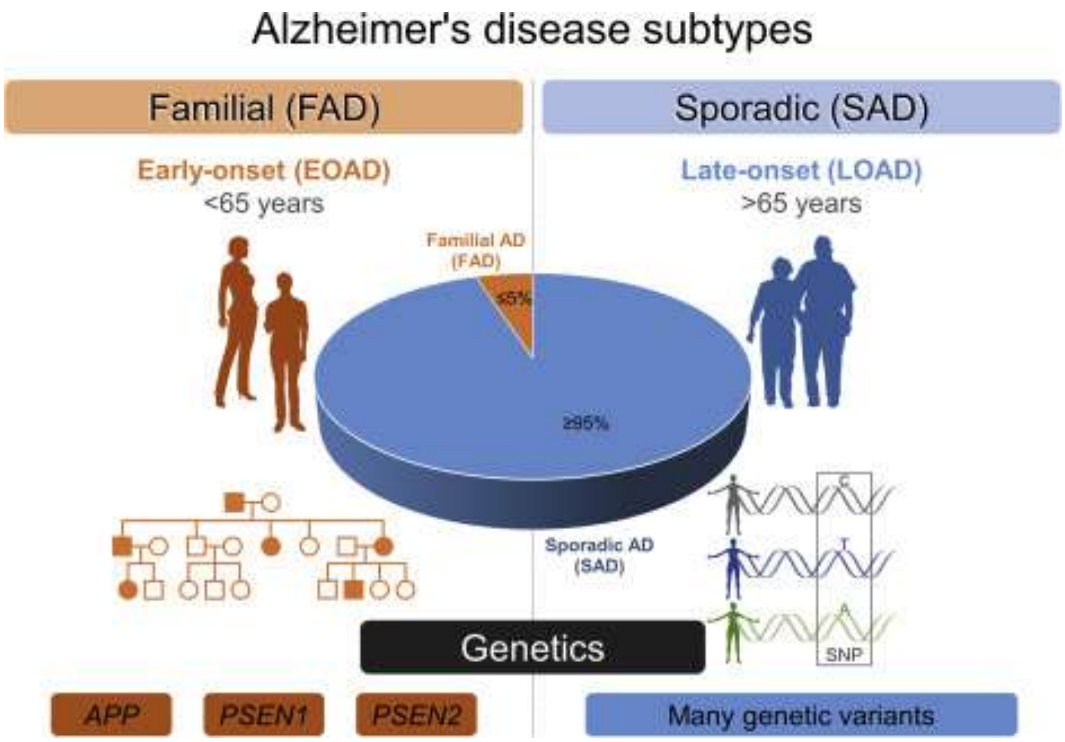

Figure 1. Familial (fAD) and sporadic (sAD) are the two forms of Alzheimer's disease in the general population. fAD occurs in around 5% of cases and is caused by known genetic mutations. sAD occurs in approximately 95% of cases and the exact causes of this form are not known.

Familial Alzheimer's disease is the early onset form of the disease, typically occurring in individuals younger than 65. Familial Alzheimer's disease is caused by inherited mutations in the *APP, PSEN1,* or *PSEN2* genes. These genetic mutations directly interfere with how the Amyloid Precursor Protein (APP) is processed in the brain (Figure 2). In a healthy brain, APP is a protein processed on the cell surface that helps establish and maintain connections between neurons. In Alzheimer's disease, APP is transported into the cell before it can be processed on the cell surface. APP inside the cell is processed differently and leads to the accumulation of amyloid-beta which is toxic to cells. In both cases, APP is processed or cut by enzymes known as secretases, but the secretases and where they cut are different between a healthy brain and Alzheimer's disease.

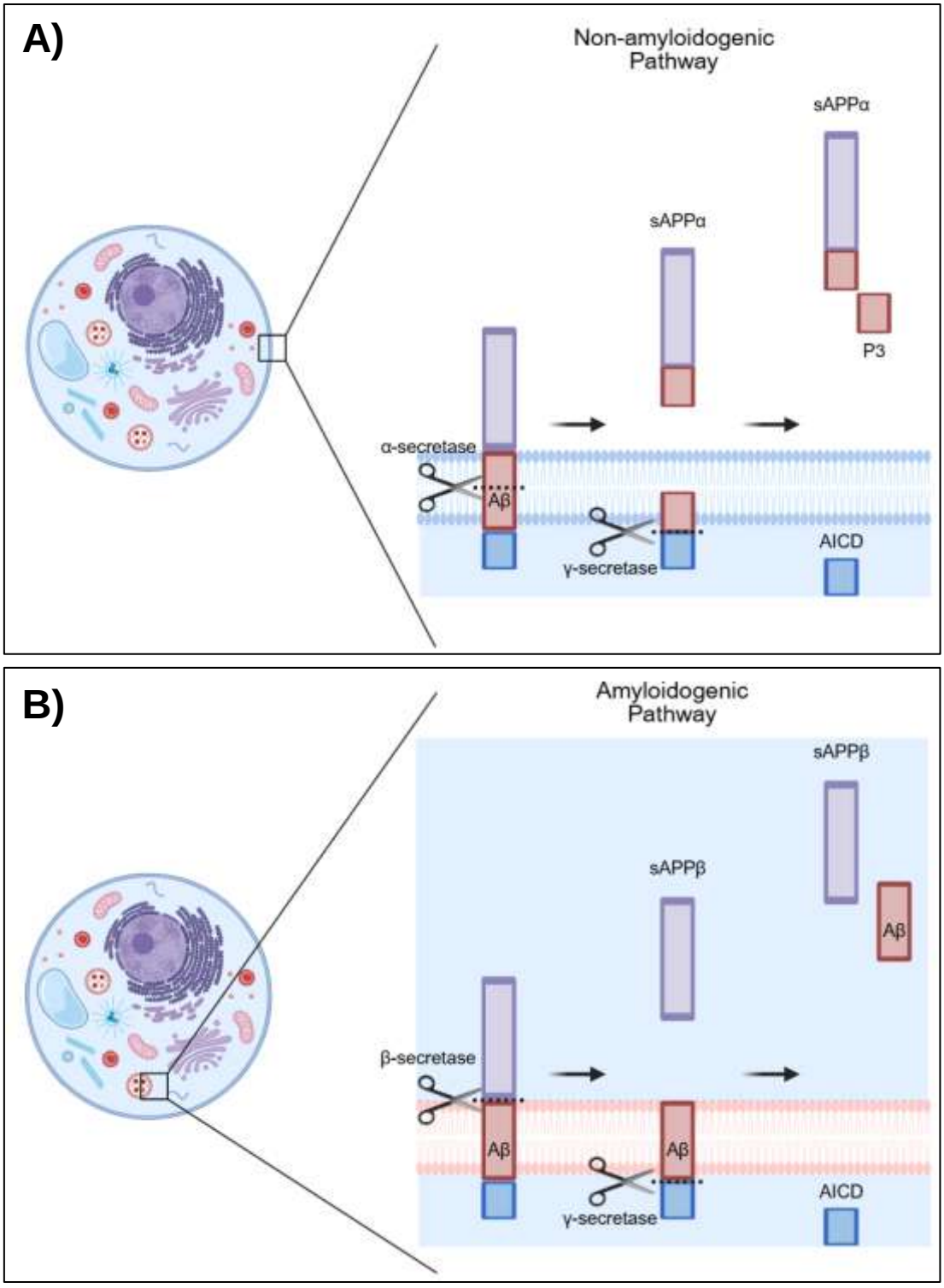

Figure 2. Processing of the Amyloid Precursor Protein (APP). A) Under normal healthy conditions APP is processed by the non-amyloidogenic pathway. This pathway cuts APP into fragments that perform normal functions in the cell and are not toxic. B) In Alzheimer's disease, APP is processed by the amyloidogenic pathway. This pathway cuts APP into fragments known as amyloid-beta (Aβ). Aβ accumulates into structures called amyloid plaques which are toxic to cells.

In a healthy brain, APP is processed by the non-amyloidogenic pathway (Figure 2A). In the non-amyloidogenic pathway, APP is first cut by the enzyme alpha secretase (α-secretase) in the middle of the amyloid-beta region (red) so amyloid-beta, the toxic species, cannot form. The fragment that is cut off by alpha secretase is known as soluble APP (sAPPα; purple and red) which helps stabilize the connection between cells. The remaining piece of APP is then cut by the enzyme gamma secretase (γ-secretase) between the remainder of the amyloid-beta region (red) and the intracellular domain (blue). This cut yields a piece known as the P3 peptide (red) and a piece known as the intracellular domain (AICD). The role of the P3 peptide (red) is not well understood. The intracellular domain (blue) travels into the nucleus of the cell and promotes expression of genes necessary for neuron maintenance and function.

In Alzheimer's disease, more APP is transported inside the cell before it can be processed at the cell surface. When APP is processed inside the cell, it is more likely to be processed by the amyloidogenic pathway (Figure 2B). In this pathway, APP is first cut by beta secretase (β-secretase) between the amyloid-beta region (red) and the extracellular domain (purple). When gamma secretase (γ-secretase) makes the next cut between the amyloid-beta region (red) and the intracellular domain (blue), the full-length red piece is amyloid-beta (Aβ). Amyloid-beta accumulates and clumps together, forming structures called amyloid plaques that are almost impossible for cells to clear. These amyloid plaques are toxic to brain cells and are a key feature of Alzheimer's disease.

Sporadic Alzheimer's disease typically occurs in individuals 65 and older. Sporadic Alzheimer's disease also results in the accumulation of amyloid plaques. Unlike familial Alzheimer's disease which has known genetic mutations that interfere with the processing

of APP, we don't know exactly what causes the sporadic form of the disease. There are several risk factors that increase the likelihood of developing sporadic Alzheimer's disease, such as age, smoking, obesity, and variations in some genes. However, none of the risk factors guarantee a person will develop sporadic Alzheimer's disease, showing that the disease is complex and likely results from a combination of genetic factors, environmental exposures and lifestyle choices[3,4].

Memory loss in Alzheimer's disease

While you can probably tell me the name of your best friend instantly, you'll likely have a harder time remembering the name of your 9th grade math teacher. That is because you talk to your best friend frequently but haven't talked to your math teacher in years. Responsible for these memories are the connections made by cells in our brains, specifically the neurons. Neurons are the messenger cells in our brain which communicate with other neurons and cells throughout the body using chemical messengers and electrical signals.

When we learn something new, connections form between a group of neurons. Those same neurons are activated every time we recall that piece of information, and each recall strengthens those connections. Think of recalling a memory like driving from your house to the grocery store where you are the information traveling between neurons. Recalling your best friend's name is like driving on a well-maintained highway. The road is easy to drive on, and you will get to your destination quickly. Information gets easier to remember the more we use it because the connection between the neurons is stronger, making it easier and faster for the information to travel. Recalling your 9th grade math teacher's name is like driving on a poorly maintained road with many traffic lights. The

traffic lights and poor road conditions will slow you down, and it will take you longer to reach your destination. The connections between neurons weakens for information that we don’t use frequently making it harder to remember.

The memory loss in Alzheimer's disease is like the road between your house and the grocery store being under construction. Early stages of Alzheimer's disease are like the road still being open during construction. Traffic will slow down due to the construction zone and changing traffic patterns, but you can still get to the grocery store. During the early stages of Alzheimer's disease, the connections between the neurons are weakening, making information harder and slower to recall. The later stages of the disease are like the road being completely closed during construction so you can no longer travel between your house and the grocery store. The memory loss is caused by neuron death and the loss of the connections. Neurons continue to die as the disease progresses. The travel of information through the brain gets harder and harder as neurons die. Eventually the information can no longer travel through the brain and the memory is lost[5].

Neuron loss in Alzheimer's disease

Neurons die in Alzheimer's disease due to the accumulation of misfolded proteins in the brain. Proteins are molecules that are critical for cells to function. Some functions of proteins include providing structure to cells, transporting signals between cells, breaking down nutrients in the food you eat for energy, and protecting your body from things like bacteria and viruses. Each protein needs to fold into a specific shape to do its job. If the protein misfolds, it can’t work correctly, and the cell will not be able to perform the functions necessary for it to stay alive[6].

Amyloid-beta and TAU are the two major proteins that misfold and accumulate in Alzheimer's disease. Amyloid-beta is a cleavage product that occurs when the Amyloid Precursor Protein is not processed correctly (Figure 2). Amyloid-beta does not fold correctly and cannot function properly. Amyloid-beta aggregates together and forms amyloid plaques. These plaques are not easily cleared from the brain, and as they accumulate they become toxic to cells[7].

TAU is a protein that helps cells keep their shape by stabilizing support structures called microtubules (Figure 3). In Alzheimer's disease, the TAU protein undergoes a chemical change called phosphorylation, where a phosphate group is added to it. This change prevents TAU from attaching correctly to microtubules, weakening the cell's internal support system and disrupting the movement of materials inside the cell. Phosphorylated TAU accumulates into structures called TAU oligomers. These TAU oligomers are toxic to cells and can easily be spread from cell to cell. TAU oligomers can aggregate into neurofibrillary tangles (NFTs). Scientists are finding that the NFTs might not directly kill cells, but they still trap the TAU protein, which prevents the cells from doing their jobs the way they should[7].

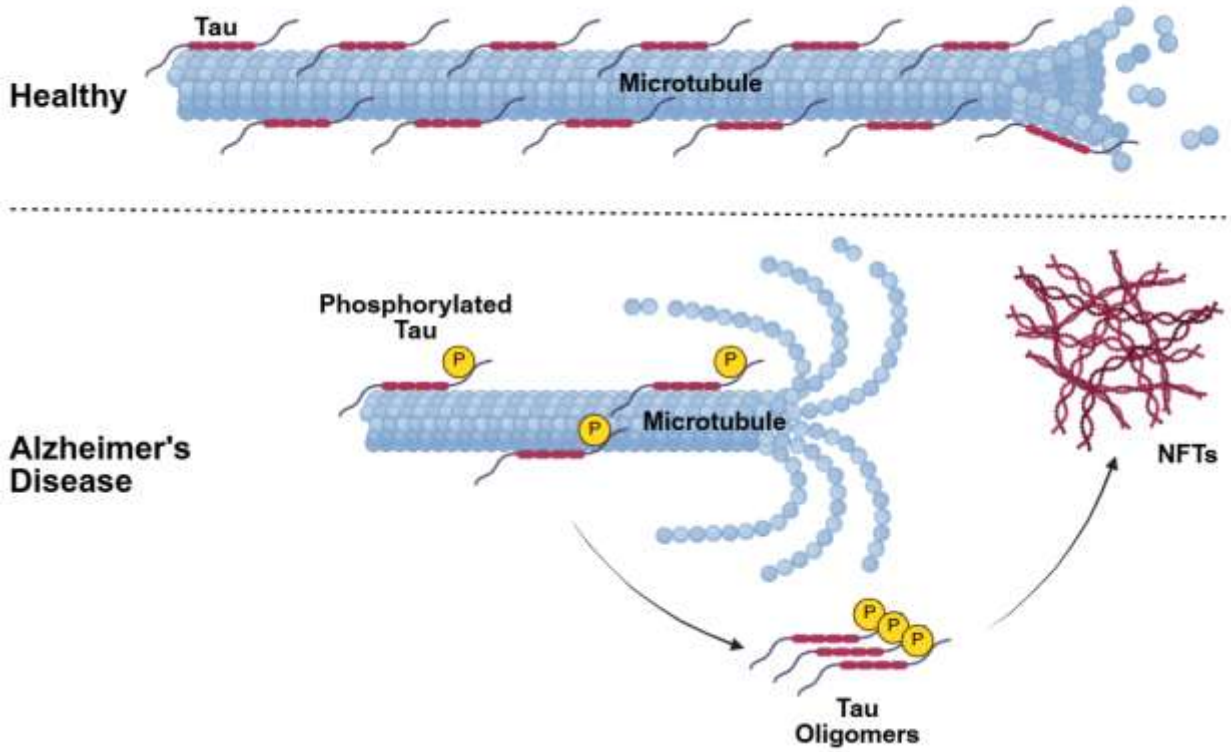

Figure 3. In a healthy brain, the TAU protein stabilizes microtubules. Microtubules provide structural support and allow materials to be transported throughout the cell. In Alzheimer's disease, the TAU protein is phosphorylated and prevents TAU from attaching correctly to microtubules. Without TAU to stabilize them, the cell's microtubules fall apart, which weakens the cell's internal framework and interferes with the transport of essential materials within the cell. Phosphorylated TAU accumulates into structures called TAU oligomers, which are toxic to cells. TAU oligomers can accumulate into neurofibrillary tangles (NFTs). NFTs are not directly toxic to cells, but they trap the TAU protein and prevent the cell from functioning properly.

Over many years, the brain of a person with Alzheimer's disease slowly fills up with harmful structures—amyloid plaques, TAU oligomers, and NFTs. As the harmful structures buildup, they interfere with how neurons work, and eventually the neurons can no longer survive. Memory loss and other symptoms slowly get worse over time as more and more neurons in the brain stop working and eventually die. Even though we understand what Alzheimer's disease does to the brain—and in some cases what triggers

it—current treatments are still very limited. Current treatments offer limited help for symptoms like memory issues, but the treatments don't stop the disease or cure it.

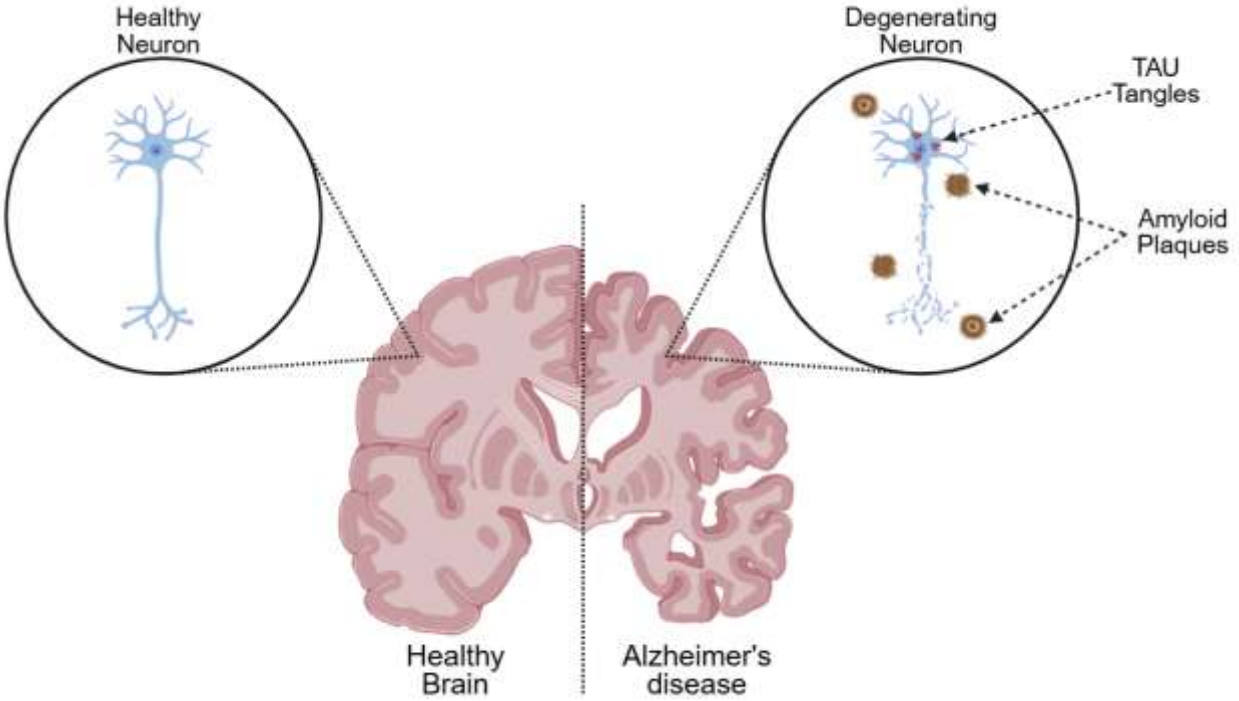

Figure 4. A healthy brain (left) and a brain from Alzheimer's disease (right). Amyloid plaques and TAU tangles (NFTs) accumulate in the Alzheimer's disease brain over time. These pathological structures inhibit neurons from functioning properly, and eventually the neurons begin to degenerate and die.

Down syndrome

Down syndrome is considered a unique form of Alzheimer's disease (often called DS-AD). Down syndrome occurs when a person is born with an extra copy of chromosome 21. Instead of the usual two copies, they have three (Figure 5). That extra chromosome adds extra copies of certain genes, which can affect how the brain and other organs develop[8]. Two important genes linked to Alzheimer's disease—*APP* and *DYRK1A* (which adds phosphate groups to TAU)—are located on chromosome 21. Because of the extra copies of the genes, people with Down syndrome naturally produce more of these

proteins, which increases their risk of developing Alzheimer's-related changes in the brain[9].

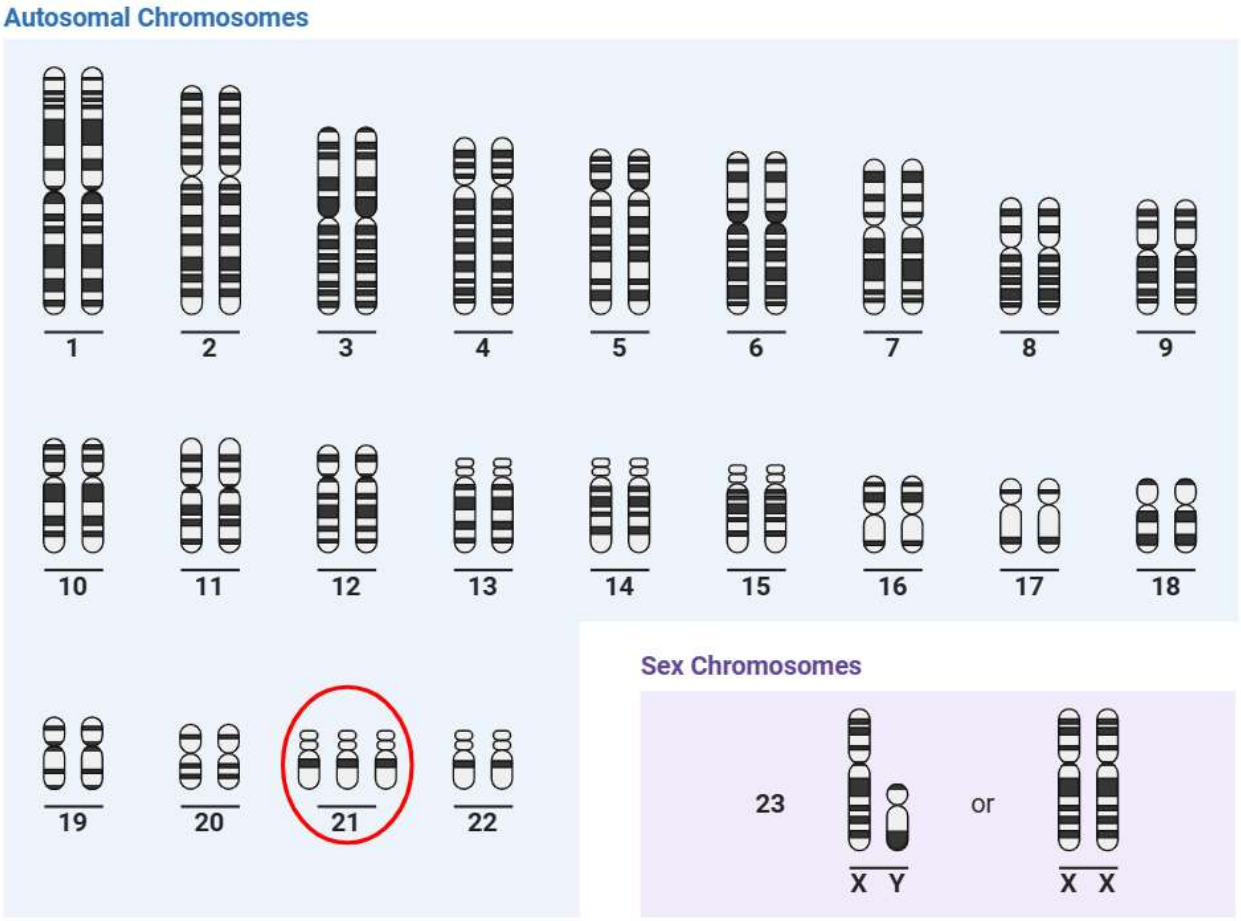

Figure 5. Humans have 46 chromosomes in total—22 pairs plus two sex chromosomes. People with Down syndrome have an extra copy of chromosome 21, giving them three instead of the usual two copies. This additional chromosome can influence how the brain and other organs develop and can affect health throughout life.

Over 90% of individuals with Down syndrome will develop Alzheimer's disease in their lifetime and they develop it earlier than the general population. For people with Down syndrome, disease onset and symptoms begin in their early to mid-50s, compared to age 65 or older in the general population[10]. The same kinds of brain changes seen in Alzheimer's disease also appear in people with Down syndrome, but they tend to show up much earlier in life (Figures 6 and 7).

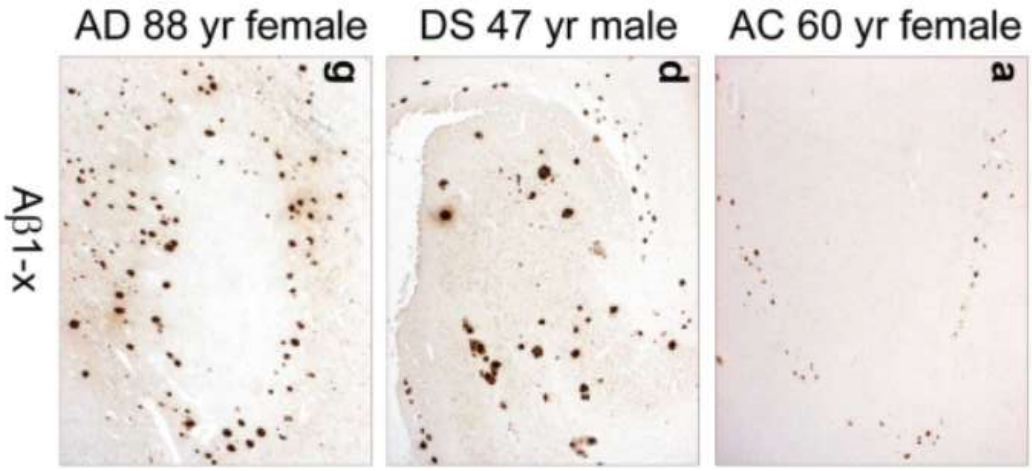

Figure 6. Amyloid plaques (dark brown) in the brains of an 88-year-old with sporadic Alzheimer's disease (left), a 47-year-old individual with Down syndrome (middle), and a 60-year-old healthy control (right). Amyloid plaques accumulate in the Down syndrome brain much earlier than in the general population.

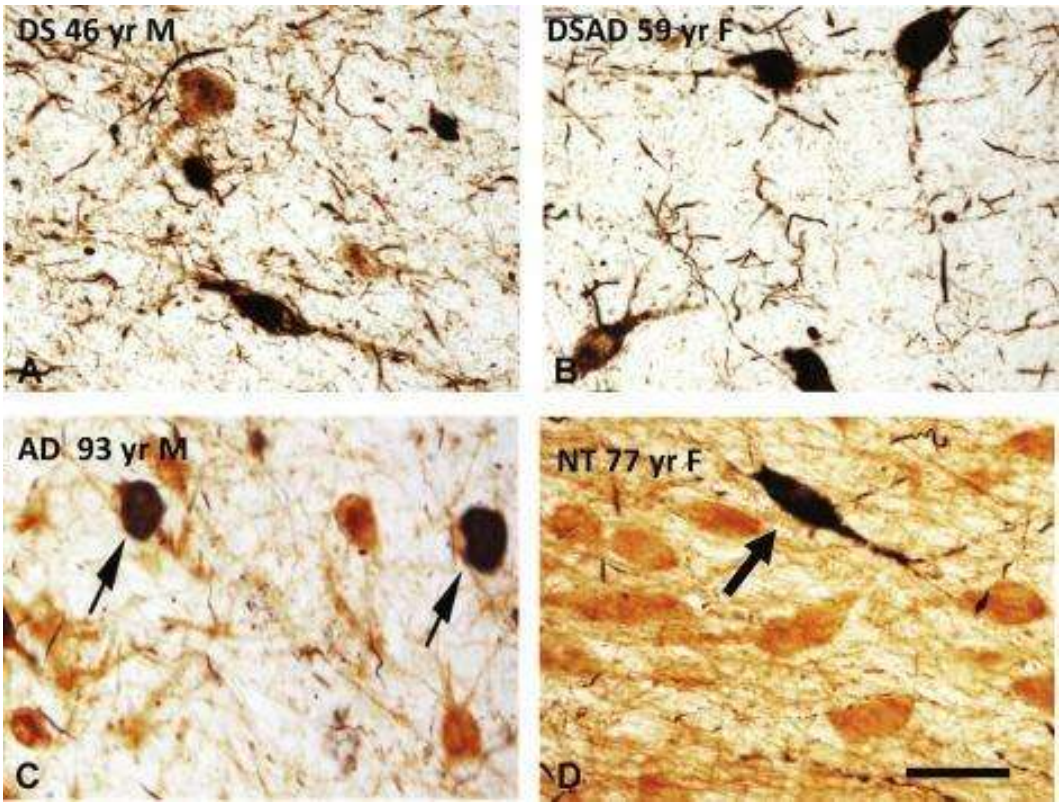

Figure 7. Phosphorylated TAU (black) and neurons (brown) in the brains of a 46-year-old with Down syndrome (top left), a 59-year-old individual with Down syndrome and Alzheimer's disease (top right), a 93-year-old with sporadic Alzheimer's disease (bottom left), and a 77-year-old healthy control (bottom right). Phosphorylated TAU accumulates in the Down syndrome brain much earlier than in the general population.

Even though Alzheimer's disease is very common in people with Down syndrome, they have mostly been left out of clinical trials for new Alzheimer's treatments. Individuals with Down syndrome are often excluded because scientists and doctors worry the additional health complications common in Down syndrome could affect the safety of the treatments[11]. More research into how Alzheimer's disease progresses in people with Down syndrome will help scientists and doctors better understand which treatments might be safe and effective. With that knowledge, there's hope that people with Down syndrome will be included in future clinical trials and be approved for therapies that could improve their quality of life.

Cholinergic neurons in Down syndrome

To better understand how Alzheimer's disease develops in people with Down syndrome I focused on cholinergic neurons. Cholinergic neurons regulate learning, attention, and memory through the release of the chemical messenger, acetylcholine. In Down syndrome and Alzheimer's disease, cholinergic neurons are some of the first neurons to die. When these neurons die, there is less acetylcholine to help neurons throughout the brain communicate and retrieve information.

Cholinergic neurons begin to die in people with Down syndrome as early as their 20s with a steep decline starting around age 40[12], decades earlier than what's seen in sporadic Alzheimer's disease or in normal aging. I wanted to understand what drives the early cholinergic neuron loss in Down syndrome. Learning how these neurons die so early may help identify drug targets that could slow or even prevent their loss. Reducing the

loss of cholinergic neurons has the potential to delay memory problems and improve the quality of life for individuals with Down syndrome. Findings from this work may also apply to Alzheimer's disease and other dementias, where cholinergic neurons are similarly affected.

How are cholinergic neurons dying in Down syndrome and Alzheimer's disease?

Little research has been done to understand what is causing these cholinergic neurons to die in Down syndrome and Alzheimer's disease. One study looked at the gene expression differences in a mouse model of Down syndrome and Alzheimer's disease compared to control mice. Genes provide all of the instructional material to make proteins, which carry out all of work in a cell. Each and every gene in a cell provides instructions for a specific protein. Any change in gene expression can result in the production of too much or too little protein. The cell needs a perfect balance of all the proteins to function properly, so having too much or too little of any given protein can compromise cell function.

By comparing the gene expression between the disease mouse model and the control, a research group uncovered cell functions that are altered in cholinergic neurons in the Down syndrome mouse model. The cholinergic neurons in the Down syndrome mouse model had altered expression of genes involved in cell signaling and energy production[13]. When cell signaling is disrupted, cells are not able to effectively communicate with one another, and the breakdown in communication between cells causes changes in brain function.

Energy production is also crucial for normal cell and brain function. Too much or too little energy affects the cell's ability to carry out normal functions. Dysfunction in one cell can also impact the function of all cells it communicates with. As a safety mechanism, cells have the ability to initiate apoptosis, or programmed cell death, when they are not functioning properly. When a few cells are not functioning properly, they can initiate apoptosis and preserve the function of the rest of the cells in the network. However, whenever most of the cells in the network do not function correctly and die, that network or brain region will no longer function correctly.

We know that the extensive death of cholinergic neurons leads to memory loss in Down syndrome and Alzheimer's disease. This study revealed that the cholinergic neurons may be dying because they cannot properly communicate with one another and they cannot function properly due to changes in energy production. While this research is very important and provides insight into what could be causing the cholinergic neurons to die, this work was done in a mouse model and we need to confirm that this is actually what is happening in the human brain.

Utility and limitations of model systems

Laboratories commonly use model systems, such as rodents, cells, monkeys, and flies, to understand some aspects of human health and disease. These model systems are much more accessible than human samples. These models can be used to understand what a gene does, or how a cell functions and communicates, or to screen potential therapeutic for disease – things researchers cannot do in humans or human samples. However, these models aren't human and don't always perfectly model human

development, aging, and disease. It is important for researchers to understand what is happening in humans to ensure the model truly represents human biology. While no model system is perfect, it is important to understand their limitations and what human biology they can or cannot accurately model. Fortunately for individuals who donate their brains, researchers are able to study brain development, aging, and disease progression. The findings in humans can be compared to model systems to determine which model system best models a particular aspect of human biology.

Uncovering cholinergic neuron dysfunction in Down syndrome using human tissue

Introduction

When I started my PhD, researchers knew that cholinergic neurons die in individuals with Down syndrome and that this neuron death causes memory loss. But we didn't know what was causing these neurons to die in humans. Once neurons start dying, there are currently no treatment options that can bring them back. That is why I studied the brains of individuals with Down syndrome long before cholinergic neurons die and compared them to healthy controls.

Methods

I worked with a brain repository to get brain tissue from young individuals who donated their brains for research. Because the cholinergic neurons start dying when individuals with Down syndrome are in their 20s, understanding what is going wrong in these cells early in life could provide information on how we could save these cells from dying. If we understand early problems in how cholinergic neurons function in Down

syndrome, we may be able to treat them before it is too late and restore their normal function. Restoring the function of the cholinergic neurons could eventually prevent cell death and ultimately memory loss.

To understand what could be going wrong in the cholinergic cells in Down syndrome, I worked with Dr. Andre Sousa's laboratory to measure the gene expression in the cholinergic neurons and other brain cells – similar to what the research group did in the mouse model of Down syndrome. To measure gene expression and infer what cell functions are dysregulated, researchers can isolate RNA. RNA is the intermediate between the DNA (the gene) and the protein. The DNA stays in the nucleus at the center of the cell but proteins are made outside of the nucleus. RNA is the intermediate that is copied from the DNA and then the RNA travels outside the nucleus to provide the instructions to make the protein.

Because RNA is difficult to isolate, and samples can easily be contaminated, Dr. Masoumeh Hosseini in Dr. Sousa's laboratory isolated the RNA from my brain samples. The RNA was then sent to a company that reads the sequences of each RNA in the sample. Once the company sent back the sequences, I worked with Dr. Sara Knaack from Dr. Sousa's laboratory and Dr. Kalpana Hanthanan Arachchilage from Dr. Daifeng Wang's laboratory to determine what genes were expressed. Determining what genes are expressed is done by mapping all of the RNA sequences to the genes they come from. The number of RNA sequences that map to a particular gene provides the expression level of that gene. A lot of RNA sequences that map to a gene means that the gene is highly expressed and conversely few RNA sequences that map to a gene means that the gene is barely expressed. I then compared gene expression patterns in the

cholinergic neurons from individuals with Down syndrome with those from healthy controls. By finding out which genes are increased or decreased, we can determine what cellular processes might be affected in the cholinergic neurons in Down syndrome.

Results

I found that genes involved in energy production are increased in Down syndrome cholinergic neurons[14]. Mitochondria are small compartments in the cell that generate most of the cell's energy in the form of adenosine triphosphate (ATP) (Figure 8). Several of the genes involved in the production of ATP are increased in Down syndrome cholinergic neurons. While more energy might seem like a good thing, it can actually cause problems in the cell. Reactive oxygen species (ROS) are generated as a byproduct of ATP production. These ROS can cause cellular damage if they are not broken down by the cell. Under normal conditions, cells break down these ROS into molecules that are not harmful to cells. However, if energy production is increased, there is more ROS. If the cell is not able to break these ROS down quick enough, the buildup of ROS will cause cellular damage. ROS can damage many parts of a cell, including DNA, proteins, and lipids. DNA holds the instructions a cell needs to function, proteins do most of the work in the cell, and lipids form the cell's outer membrane, which controls what enters and leaves the cell. When ROS damages these components, the cell can't function properly and becomes more vulnerable to cell death. I think that cholinergic neurons in Down syndrome produce too much energy and generate excess reactive oxygen species, leading to cellular damage and ultimately cell death.

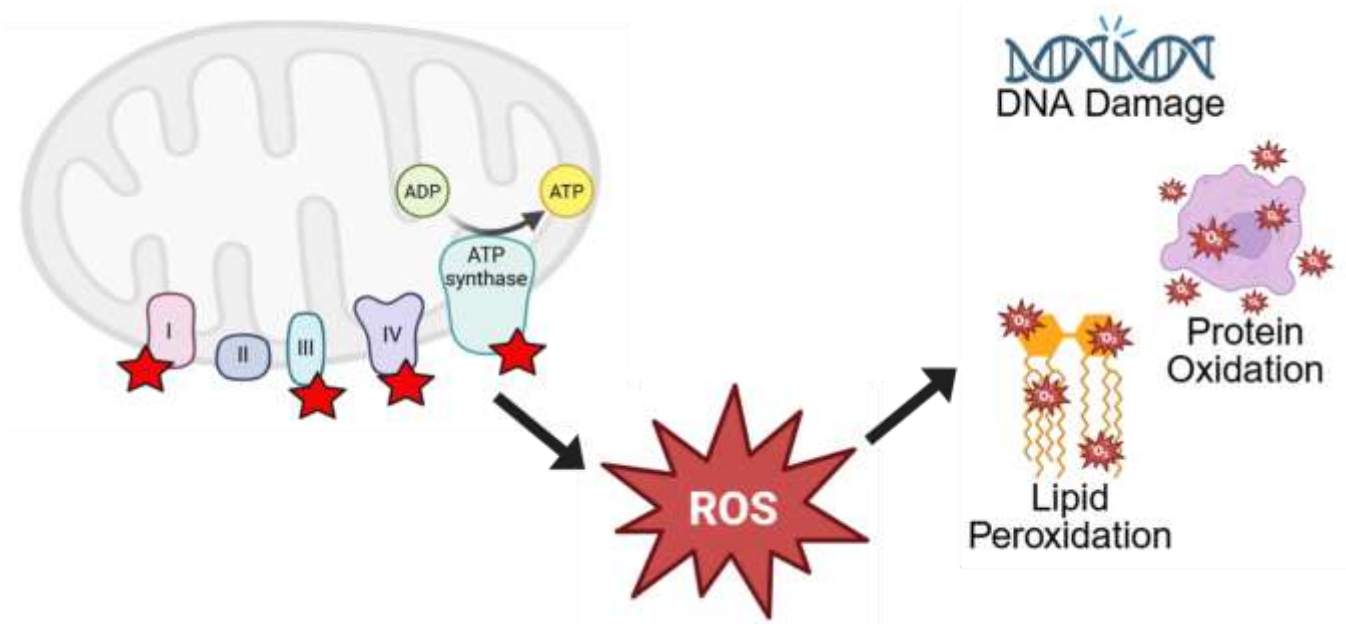

Figure 8. Mitochondria generate most of the cell's energy in the form of adenosine triphosphate (ATP). Reactive oxygen species (ROS) are generated as a byproduct of ATP production. These ROS can cause cellular damage if they are not broken down by the cell. ROS can damage DNA, proteins, and lipids. Damage to these components leave the cell unable to function properly.

Additional work is still needed

With this work, we are one step closer to understanding what could be going wrong in Down syndrome cholinergic neurons. But we are not ready to start clinical trials just yet. Additional work is needed to prove that regulating the energy production in these cholinergic neurons would stop them from dying. It is likely that we have only solved a small piece of a larger puzzle. Other factors could also contribute to cholinergic neuron death. We need to put the entire puzzle together and understand all the reasons behind the cellular dysfunction before we can design safe and effective treatments. But with each new piece we uncover, we are closer to developing treatments that could delay memory problems in Down syndrome, Alzheimer's disease, and other forms of dementia.

References

1 Hippius, H. & Neundörfer, G. The discovery of Alzheimer's disease. *Dialogues Clin Neurosci* 5, 101-108 (2003). https://doi.org:10.31887/DCNS.2003.5.1/hhippius

2 *Alzheimer's Disease*, <https://my.clevelandclinic.org/health/diseases/9164-alzheimers-disease> (2025).

3 Aulston, B. *What is Familial Alzheimer's Disease?*, <https://www.brightfocus.org/resource/what-is-familial-alzheimers-disease/> (2021).

4 *Alzheimer's disease*, <https://www.nhs.uk/conditions/alzheimers-disease/causes/#:~:text=Alzheimer's%20disease%20is%20thought%20to,form%20plaques%20around%20brain%20cells.> (2024).

5 *Inside the Science of Memory*, <https://www.hopkinsmedicine.org/health/wellness-and-prevention/inside-the-science-of-memory> (2026).

6 *Proteins*, <https://my.clevelandclinic.org/health/body/proteins> (2025).

7 Findley, C. *What are Alzheimer's Plaques and Tangles?*, <https://www.brightfocus.org/resource/what-are-alzheimers-plaques-and-tangles/> (2024).

8 *Down syndrome*, <https://www.mayoclinic.org/diseases-conditions/down-syndrome/symptoms-causes/syc-20355977> (2026).

9 *Alzheimer's Disease & Down Syndrome*, <https://ndss.org/resources/alzheimers> (2026).

10 Fortea, J. *et al.* Alzheimer's disease associated with Down syndrome: a genetic form of dementia. *The Lancet Neurology* 20, 930-942 (2021). https://doi.org:10.1016/S1474-4422(21)00245-3

11 Strydom, A. *et al.* Alzheimer's disease in Down syndrome: An overlooked population for prevention trials. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 4, 703-713 (2018). https://doi.org:https://doi.org/10.1016/j.trci.2018.10.006

12 Rozalem Aranha, M. *et al.* Basal forebrain atrophy along the Alzheimer's disease continuum in adults with Down syndrome. *Alzheimers Dement* 19, 4817-4827 (2023). https://doi.org:10.1002/alz.12999

13 Alldred, M. J. *et al.* Profiling Basal Forebrain Cholinergic Neurons Reveals a Molecular Basis for Vulnerability Within the Ts65Dn Model of Down Syndrome and

Alzheimer's Disease. *Mol Neurobiol* 58, 5141-5162 (2021). https://doi.org:10.1007/s12035-021-02453-3

14 West, N. R. *et al.* Single-nucleus analysis reveals oxidative stress in Down syndrome basal forebrain neurons at birth. *Alzheimers Dement* 21, e70445 (2025). https://doi.org:10.1002/alz.70445

Figure References

Figure 1) Castanho, I. & Lunnon, K. in *Chromatin Signaling and Neurological Disorders* Vol. 12 (ed Olivier Binda) 153-180 (Academic Press, 2019).

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Figure 6) Kumar, S., Lemere, C. A. & Walter, J. Phosphorylated Aβ peptides in human Down syndrome brain and different Alzheimer's-like mouse models. *Acta Neuropathologica Communications* 8, 118 (2020). https://doi.org:10.1186/s40478-020-00959-w

Figure 7) Mufson, E. J. & Perez, S. E. in *Handbook of Clinical Neurology* Vol. 211 (ed A. Claudio Cuello) 185-213 (Elsevier, 2025).
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