

Chapter 13: The Aging Brain and Neurodegeneration

Summary

Every brain changes with age, but dementia is not a normal part of aging. This chapter separates normal brain aging from **neurodegeneration**, the slow death of neurons that causes Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease. You will see how misfolded proteins clump into plaques and tangles, how biomarkers reveal disease years before symptoms, and what new medicines (anti-amyloid antibodies, antisense drugs, and gene therapy) can and cannot do.

Concepts Covered

1. Normal Brain Aging
2. Neurodegeneration
3. Protein Misfolding
4. Dementia
5. Alzheimer's Disease
6. Amyloid Plaque
7. Tau Tangle
8. Anti-Amyloid Antibody
9. Amyotrophic Lateral Sclerosis
10. Huntington's Disease
11. Antisense Oligonucleotide
12. Gene Therapy
13. Biomarker
14. Cognitive Reserve

Prerequisites

- [Chapter 1: Neurons, Glia, and the Nervous System](#)
- [Chapter 2: The Action Potential](#)
- [Chapter 3: Synapses and Neurotransmitters](#)
- [Chapter 4: A Tour of the Brain](#)
- [Chapter 7: Movement](#)
- [Chapter 9: Learning, Memory, and Neuroplasticity](#)

Brains that last a lifetime



I'm a sea slug, so I don't live long enough to worry about getting old. You will, and so will everyone you love. This chapter is about telling ordinary forgetfulness apart from disease, and about some of the newest medicines in neurology. By the end, you'll be able to read a headline about an "Alzheimer's breakthrough" and judge what it really means.

13.1 Is Forgetting My Name Normal?

Maya is home from soccer practice, studying Brain Bee flashcards at the kitchen table, when her grandfather comes to visit. He hugs her and says, "Good to see you, Priya." Priya is Maya's mom. He laughs it off. But later he asks Maya the same question about her team three times in one hour, and her mom mentions that he recently got lost driving to a grocery store he has used for twenty years.

Is this just what happens when people get old, or is something wrong with his brain? Families ask doctors this every day, and the answer can change a person's care and safety. To answer it, start with what a *healthy* aging brain looks like.

13.2 Normal Brain Aging

Think of your brain as a library that has been open for 80 years. The books are still there, but the librarians walk slower and finding a book takes longer. Almost everything still works. It

just takes more time.

That's **normal brain aging**: the gradual, expected changes in brain structure and thinking that happen as healthy people grow older, without disease. According to the [National Institute on Aging \(NIA\)](#), as people age:

- certain brain regions shrink, including some that are important for learning and complex thinking
- communication between neurons in some regions becomes less efficient
- blood flow in the brain may decrease
- inflammation may increase

These changes show up as slower thinking. An older adult may take longer to find a word or recall a name, find multitasking harder, or have small drops in attention. The good news is that older adults often have *larger* vocabularies than younger adults, and given enough time, they usually learn new tasks just as well.

The healthy aging brain shrinks somewhat, but it **does not lose neurons in large numbers**. That makes it very different from the diseases in the rest of this chapter.

Normal forgetting versus dementia

To tell normal aging from disease, doctors ask whether the memory or thinking problem **interferes with everyday life**. Forgetting a word now and then is normal. Getting lost on a familiar route, as Maya's grandfather did, is a warning sign. The table below sums up comparisons the [NIA](#) uses with families.

Normal aging	Possible sign of dementia
Making a bad decision once in a while	Making poor judgments much of the time
Missing one monthly payment	Having trouble managing bills at all
Forgetting which day it is, then remembering later	Losing track of the date or the season
Sometimes forgetting which word to use	Trouble following or having a conversation

Normal aging	Possible sign of dementia
Losing things from time to time	Misplacing things often and being unable to find them

Memory problems can also come from treatable causes, such as depression, thyroid problems, low vitamin B12, medication side effects, or poor sleep. That's one reason to see a doctor instead of assuming it's "just age."

13.3 When Neurons Die: Neurodegeneration and Protein Misfolding

Neurodegeneration is the progressive loss of the structure and function of neurons, ending in neuron death. "Progressive" means it keeps getting worse over time. Most neurons are never replaced. A dead skin cell is swapped for a new one, but a neuron that dies in your hippocampus or spinal cord is usually gone for good.

An origami problem

A protein is like a strip of paper folded into an exact origami shape. The shape is everything: a crane can "fly," but a crumpled ball of the same paper can't do anything. Cells fold every protein carefully into its working shape.

Protein misfolding is when a protein folds into the wrong shape. Misfolded proteins tend to be "sticky." They cling to each other and form clumps that cells struggle to clear, and over time the clumps damage the cell. Many very different brain diseases share this problem, as the table below shows. Each one has its own protein, its own target neurons, and its own symptoms.

Disease	Misfolded or toxic protein	Main neurons or region hit	First big symptoms
Alzheimer's disease	Beta-amyloid (outside cells) and tau (inside cells)	Hippocampus and entorhinal cortex first, then cortex	Memory loss

Disease	Misfolded or toxic protein	Main neurons or region hit	First big symptoms
Parkinson's disease (Chapter 7)	Alpha-synuclein (Lewy bodies)	Dopamine neurons of the substantia nigra	Slow movement, tremor
ALS (SOD1 type)	Misfolded SOD1	Motor neurons	Weakness, twitching
Huntington's disease	Abnormally long huntingtin protein, cut into toxic fragments	Striatum (part of the basal ganglia)	Uncontrolled movements, mood changes

Same mistake, different neighborhoods



The big idea of this chapter: many neurodegenerative diseases are "the wrong protein, piling up in the wrong place." Where the pile builds up decides whether a person first loses memory, movement, or muscle strength.

13.4 Dementia and Alzheimer's Disease

Dementia is not one disease. It is a general term for a loss of thinking, remembering, and reasoning severe enough to interfere with a person's daily life and activities ([NIA](#)). Some people with dementia also have trouble controlling emotions, or their personality changes. Dementia becomes more common with age: the NIA estimates that about one-third of people age 85 or older may have some form of it. But dementia is **not a normal part of aging**, and many people live into their 90s and beyond without any signs of it.

Dementia has many causes, including vascular dementia (from damaged blood vessels; see [Chapter 14](#)), Lewy body dementia, and frontotemporal dementia. The most common cause in older adults is **Alzheimer's disease**: a progressive brain disease that slowly destroys memory and thinking skills and, eventually, the ability to carry out simple tasks. According to the [NIA fact sheet](#), estimates vary, but more than 6 million Americans, most of them 65

or older, may have Alzheimer's disease. The [Alzheimer's Association's 2026 Facts and Figures report](#) estimates that 7.4 million Americans age 65 and older are living with Alzheimer's in 2026, about 1 in 9 people in that age group.

A doctor, a microscope, and 1906

The disease is named after Dr. Alois Alzheimer. In 1906, he studied the brain of a woman who had died of an unusual mental illness that included memory loss, language problems, and unpredictable behavior. Under his microscope he saw abnormal clumps between cells and tangled bundles of fibers inside cells. Today we call them **amyloid plaques** and **tau tangles**, and more than a century later they are still the defining features of the disease.

Where Alzheimer's starts

Alzheimer's disease usually damages the **entorhinal cortex** and **hippocampus** first ([NIA](#)). You met the hippocampus in [Chapter 9](#) as the structure that turns new experiences into lasting memories. That explains the classic first symptom: trouble forming *new* memories. A person may recall their wedding day but not that they already asked you a question. Later, the damage spreads to areas of the cortex used for language, reasoning, and social behavior. In the final stage, the brain has shrunk a great deal and the person depends on others for all care.

Many people pass through an in-between stage first. In **mild cognitive impairment (MCI)**, a person has more memory or thinking problems than is normal for their age but can still manage daily life. People with MCI have a higher risk of developing Alzheimer's disease, but not all of them do, and some even return to normal thinking.

13.5 Plaques and Tangles: Inside the Alzheimer's Brain

Amyloid plaques: trash piling up outside the cell

Brain cells make a larger protein called amyloid precursor protein. When it is cut up, one of the small pieces is **beta-amyloid**. One form, beta-amyloid 42, is thought to be especially toxic ([NIA](#)). In Alzheimer's disease, too much beta-amyloid clumps together *between* neurons. An **amyloid plaque** is one of these dense clumps of misfolded beta-amyloid outside cells. Plaques sit among synapses and disrupt how neurons function.

Tau tangles: a collapsed railroad inside the cell

Every neuron has a transport system. Long tubes called **microtubules** work like railroad tracks, carrying nutrients and other cargo from the cell body down the axon (the long fiber you met in [Chapter 1](#)). A protein called **tau** acts like the railroad ties that hold the tracks steady.

In Alzheimer's disease, chemical changes make tau let go of the microtubules. The loose tau sticks to other tau, forming threads that join into **neurofibrillary tangles**. A **tau tangle** is one of these twisted clumps of abnormal tau *inside* a neuron. With the tracks falling apart, cargo can't reach the synapses, and communication between neurons breaks down. Research summarized by the NIA suggests that when beta-amyloid builds up to a kind of tipping point, abnormal tau spreads rapidly through the brain.

The rest of the damage

The NIA describes other processes that add to the damage:

- **Synapse loss.** Losing synapses ([Chapter 3](#)) is one of the earliest signs linked to cognitive decline.
- **Glia that stop helping.** Microglia normally clear waste, including beta-amyloid. In Alzheimer's disease they may fail at this and instead release chemicals that cause long-lasting inflammation.
- **Blood vessel problems.** High blood pressure, diabetes, and small strokes can reduce blood flow and add to the damage.
- **Brain shrinkage.** As neurons die, regions shrink, a process called brain atrophy.

Genes and Alzheimer's disease

Most Alzheimer's disease appears after age 65 and doesn't follow a simple inheritance pattern. A small number of cases begin much earlier, between a person's 30s and mid-60s. According to [MedlinePlus Genetics](#), some early-onset cases are caused by variants in the *APP*, *PSEN1*, or *PSEN2* genes. These variants lead to extra beta-amyloid, and they are passed down in an **autosomal dominant** pattern, meaning one altered copy of the gene is enough to cause the disease.

For the common late-onset form, the best-studied gene is *APOE*. A version called **APOE e4** raises a person's risk, and two copies raise it more. But APOE e4 is a risk factor, not a sentence. Some people with Alzheimer's disease don't carry it, and many carriers never develop the disease.

13.6 Biomarkers: Seeing Disease Before Symptoms

A **biomarker** is something measured in the body that signals a normal process, a disease process, or the body's response to a treatment. Blood sugar, for example, is a biomarker for diabetes. Brain biomarkers let doctors "see" inside the brain without opening the skull.

For a long time, the only sure way to diagnose Alzheimer's disease was to look at brain tissue after death. Now doctors can detect its biomarkers in living people:

- **Amyloid PET scan.** A small amount of a radioactive tracer that sticks to amyloid is injected into a vein. A PET scanner then shows where amyloid has built up.
- **Cerebrospinal fluid (CSF) tests.** A sample of the fluid around the brain and spinal cord, taken with a needle in the lower back (a lumbar puncture), can show amyloid and tau levels.
- **Blood tests.** On May 16, 2025, the FDA cleared the [first blood test used to help diagnose Alzheimer's disease](#). It measures the ratio of two proteins in blood (a form of tau called pTau217, and beta-amyloid 42) to help detect amyloid plaques. It is cleared for adults 55 and older who already have symptoms, and results must be read along with other clinical information. More blood tests have been cleared since then, including Roche's Elecsys pTau181 in October 2025 ([NeurologyLive](#)), and Roche's Elecsys pTau217 and C2N's PrecivityAD2 in August 2026 ([Psychiatric News](#)). As of 2026, all of them are cleared to help evaluate people who already have memory or thinking symptoms, not to screen healthy people.

Why timing is everything

Biomarker research showed that **the brain changes start long before the symptoms**. The NIA says changes may begin [a decade or more before symptoms appear](#).

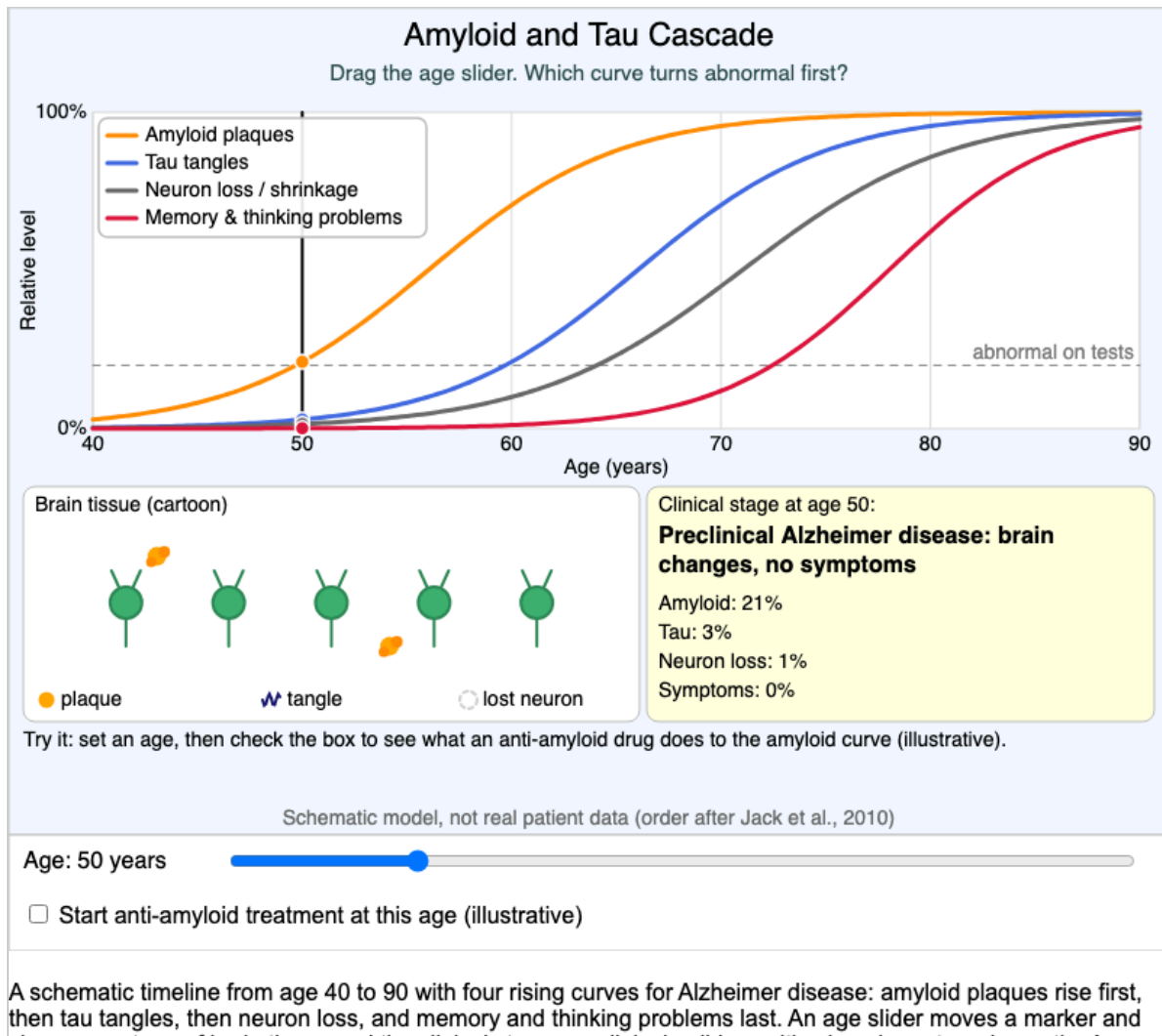
In 2010, Clifford Jack and colleagues proposed a widely cited [hypothetical model of Alzheimer's biomarkers](#). In their model, amyloid biomarkers turn abnormal first, while the

person still thinks normally. After a delay that differs from person to person, markers of neuron injury (such as tau and brain shrinkage on MRI) turn abnormal. Symptoms come last. The authors estimated that in people who later develop dementia, amyloid buildup might begin as much as two decades before symptoms. They also noted that roughly 20 to 40 percent of older adults with normal thinking already have significant amyloid in their brains.

This adds a new stage of disease. **Preclinical Alzheimer's disease** is the stage when biomarkers show Alzheimer's brain changes but the person has no symptoms yet. The stages with symptoms are mild cognitive impairment and dementia.

Experts still disagree about what to call this stage. In June 2024, an Alzheimer's Association workgroup published [revised criteria](#) that define Alzheimer's disease *biologically*: it begins when Alzheimer's brain changes appear, even before symptoms. The same workgroup said biomarker testing in the clinic is meant for people who have symptoms, not for healthy people. Later in 2024, the International Working Group, another expert panel, [disagreed](#). It proposed calling most people with abnormal amyloid but normal thinking "asymptomatic at risk of Alzheimer's disease," because many of them never develop symptoms. The MicroSim below lets you watch these stages unfold.

Diagram: Amyloid and Tau Cascade



Screenshot of the interactive simulation. Try it online: <https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch13-amyloid-tau-cascade/>

Open the Amyloid and Tau Cascade fullscreen

MicroSim specification: Amyloid and Tau Cascade

Type: microsim **sim-id:** ch13-amyloid-tau-cascade

Library: p5.js

Status: Implemented

Bloom Level: Understand

Bloom Verb: explain

Learning Objective: The learner will explain why Alzheimer's brain changes are best detected and treated early, using the order in which amyloid, tau, neuron loss, and symptoms rise.

Canvas: width-responsive; drawing area 570 px plus control area 80 px (iframe 652 px).

Content: Four schematic curves in relative units (0 to 100% of each curve's maximum) from age 40 to 90: amyloid plaques, tau tangles, neuron loss/shrinkage, and memory and thinking problems. A dashed line marks "abnormal on tests" at 20%. A tissue cartoon shows plaques between five neurons, tangles inside them, and faded lost neurons. A stage box shows the clinical stage and the four levels.

Controls: Age slider (min 40, max 90, step 1, default 50 years). Checkbox "Start anti-amyloid treatment at this age (illustrative)."

Rules: Curves are logistic with midpoints 56 (amyloid), 66 (tau), 71 (neuron loss), 78 (symptoms). Stage: symptoms < 15% and amyloid < 20% = no measurable changes; symptoms < 15% and amyloid >= 20% = preclinical; 15% <= symptoms < 50% = mild cognitive impairment; 50% <= symptoms < 75% = dementia (mild stage); symptoms >= 75% = dementia (moderate to severe). When treatment is on, amyloid after the start age decays with a 1.5-year time constant; other curves do not change. A message explains the evidence for treatment at the starting stage.

Provenance: Curve order from Jack et al. (2010); curve shapes and ages are illustrative. The sim is labeled "Schematic model, not real patient data."

Chapter Anchors: In the model, amyloid crosses the abnormal line at about age 50, tau at about 60, neuron loss at about 65, and symptoms at about 73. Mild cognitive impairment begins at about age 72 and dementia at about age 78.

What to try. Start at age 50. Amyloid is already crossing the "abnormal on tests" line, yet there are no symptoms. Drag the slider slowly right and watch the order: amyloid crosses the line at about age 50, tau at about 60, neuron loss at about 65, and symptoms at about 73. In this schematic model, mild cognitive impairment begins around age 72 and dementia around age 78. That's roughly 20 years of silent disease.

Next, set the age to 74 and check the treatment box. Amyloid drops, but tau has already spread and many neurons are gone, and removing amyloid doesn't bring them back. Then uncheck the box, move to age 86, start treatment again, and read the message. The ages are illustrative, and real people vary a lot. The lesson is the order of events, and why doctors want to find Alzheimer's disease early.

13.7 Anti-Amyloid Antibodies: Treatments That Target the Disease

For decades, Alzheimer's medicines could only treat symptoms. Cholinesterase inhibitors (such as donepezil) slow the breakdown of acetylcholine, a neurotransmitter important for memory, and memantine acts on glutamate signaling ([NIA](#)). They can help for a while but don't change what's happening to the neurons.

How an antibody can clean up plaques

Your immune system makes **antibodies**, Y-shaped proteins that latch onto a specific target and mark it for removal. An **anti-amyloid antibody** is a lab-made antibody, given by infusion into a vein (and for lecanemab, now also by injection under the skin), that binds to beta-amyloid and helps the brain's immune cells clear plaques away. It's like putting bright "pick me up" tags on trash so the cleanup crew (the microglia) finds it.

Two anti-amyloid antibodies are FDA-approved and available as of October 2026. (An earlier one, aducanumab, received accelerated approval in 2021, but its maker discontinued it in 2024.)

Drug	FDA status	Key trial	Who it's approved for
Lecanemab (Leqembi)	Accelerated approval January 6, 2023; converted to traditional (full) approval July 6, 2023. An under-the-skin autoinjector (Leqembi Iqlik) was approved for maintenance doses in August 2025 and for starting treatment in July 2026	Clarity AD, 1,795 participants, 18 months	Mild cognitive impairment or mild dementia due to Alzheimer's, with confirmed amyloid
Donanemab (Kisunla)	FDA approval July 2, 2024	TRAILBLAZER-ALZ 2, 1,736 participants, 76 weeks	Mild cognitive impairment or mild dementia due to Alzheimer's, with confirmed amyloid

Sources: FDA announcements for [lecanemab](#) (with the current [Leqembi prescribing information](#) for the under-the-skin form) and [donanemab](#); the [NIA](#) describes both as fully approved.

What the trials showed: real, but modest

Both drugs removed a lot of amyloid and slowed decline on memory and daily-living rating scales compared with placebo. But "slowed" is the key word.

In the [lecanemab trial](#), people's scores on an 18-point dementia rating scale (where higher means more impaired) got worse by 1.21 points over 18 months on the drug and 1.66 points on placebo. That's a difference of 0.45 points, or about 27 percent less worsening than on placebo. The researchers called it "moderately less decline." The [donanemab trial](#) showed a slowing of similar size. People on these drugs still got worse, just more slowly. Neither drug stops the disease, reverses it, or brings back lost memories.

That fits the MicroSim. By the time symptoms appear, tau has spread and many neurons have died. Removing amyloid at that point is like clearing debris after a fire: it may slow further damage, but it doesn't rebuild the rooms.

The main risk: ARIA

The most important side effect has a long name: **amyloid-related imaging abnormalities (ARIA)**. ARIA shows up on MRI scans as temporary swelling in the brain, sometimes with small spots of bleeding. Usually it causes no symptoms. When it does, they can include headache, confusion, dizziness, vision changes, or nausea. Rarely, it is serious or life-threatening ([FDA](#)). Both drugs carry a **boxed warning**, the FDA's strongest label warning, about ARIA.

In the trials, ARIA with swelling showed up on scans in 12.6 percent of people taking lecanemab and 24.0 percent of people taking donanemab. (The two trials enrolled somewhat different groups, so these numbers are not a head-to-head comparison.) People with two copies of APOE e4 have a higher risk of ARIA, so the FDA labels say to test for APOE e4 before starting treatment. Patients get regular MRI scans to watch for ARIA. In July 2025, the FDA approved a more gradual starting schedule for donanemab after a trial called TRAILBLAZER-ALZ 6 found that it lowered ARIA with swelling at 52 weeks from 24.2 percent to 15.6 percent ([NeurologyLive](#)). The boxed warning remains.

Approved does not mean cure



Watch out for two opposite mistakes. "There's nothing doctors can do for Alzheimer's" is wrong, but so is "the new drugs cure it." The honest version: anti-amyloid antibodies modestly slow decline in early-stage disease, they carry real risks, and they aren't for everyone.

Can treatment start even earlier?

If amyloid builds up for years before symptoms, would treatment in the preclinical stage work better? Large clinical trials are testing this in people who have amyloid but no symptoms, such as the [AHEAD 3-45 study](#) of lecanemab and the [TRAILBLAZER-ALZ 3 study](#) of donanemab. As of October 2026, neither has reported its main results. Until those results are in, treating people without symptoms remains experimental.

13.8 Cognitive Reserve: Why Some Brains Hold Up Better

Two people can have similar plaques and tangles, yet one has dementia and the other thinks clearly. How?

Picture two cities hit by the same storm, which knocks out some roads. A city with one road to the hospital is in trouble. A city with many side streets reroutes traffic, and most people never notice. **Cognitive reserve** is the brain's ability to cope with damage by using its networks more efficiently or by switching to backup routes, so that thinking stays normal longer.

Neuropsychologist Yaakov Stern separates two related kinds of reserve in his [2012 review](#):

- **Brain reserve:** differences in the brain's physical structure, such as size or number of neurons and synapses, that let it tolerate more damage.
- **Cognitive reserve:** differences in *how* the brain uses its networks, built up through life experiences such as education, challenging work, and mentally stimulating activities.

Reserve doesn't stop plaques from forming. It changes how much damage the brain can absorb before symptoms show. Jack and colleagues suggested this may help explain why the delay between amyloid and symptoms varies so much.

Can you build reserve? In one NIA-funded study of almost 3,000 older adults, people who practiced four or five healthy behaviors (physical activity, not smoking, not drinking heavily, a Mediterranean-style diet, and mentally stimulating activities) had a 60 percent lower risk of Alzheimer's disease than people who practiced one or none ([NIA](#)). This was an observational study, so it can't prove the habits *caused* the lower risk. The NIA also notes that high blood pressure in middle age is linked to higher dementia risk, so protecting your heart may help protect your brain.

Reserve starts now



Cognitive reserve is built over a whole lifetime, and school counts. Learning hard things, staying active, sleeping well (Chapter 10), and keeping up friendships are investments your 80-year-old self will thank you for.

13.9 Amyotrophic Lateral Sclerosis (ALS)

Now we move from memory to movement. In [Chapter 7](#), you learned that movement commands pass through two kinds of motor neurons. **Upper motor neurons** in the motor cortex send signals down to **lower motor neurons** in the brainstem and spinal cord, which connect to muscles.

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that kills motor neurons, the nerve cells that control voluntary movement and breathing. In the classic form, both upper and lower motor neurons die. ALS is also called Lou Gehrig's disease, after a famous baseball player who had it.

What ALS looks like

According to the [NINDS](#), early symptoms include muscle twitches, cramps, stiffness, weakness in an arm, leg, or the neck, and slurred speech or trouble chewing and swallowing. Symptoms most often begin between ages 55 and 75. Over time, people lose the ability to walk, use their hands, speak, swallow, and breathe without help. Most people with ALS die of respiratory failure, usually within three to five years after symptoms begin, although about 1 in 10 people live 10 years or more.

Most people with ALS can still reason and remember, so they are aware of what's happening. About 20 percent, however, also develop frontotemporal dementia, which affects personality, behavior, and language ([MedlinePlus Genetics](#)).

The two kinds of motor neuron loss produce different signs, just as in Chapter 7 ([NINDS](#)):

Damaged neurons	Signs a doctor finds
Lower motor neurons	Weakness, muscle wasting (atrophy), twitches (fasciculations)
Upper motor neurons	Stiffness (spasticity), overactive reflexes

Finding *both* sets of signs in the same patient is a big clue pointing toward ALS.

Genes and ALS

NINDS reports that nearly all ALS is **sporadic**, meaning it appears without a clear family history. About 10 percent of cases are **familial**, running in families. Mutations in a gene

called *C9orf72* cause about 25 to 40 percent of familial cases, and mutations in the *SOD1* gene cause another 12 to 20 percent. The *SOD1* gene normally makes an enzyme called superoxide dismutase, which breaks down harmful, charged oxygen molecules that cells make as by-products ([MedlinePlus Genetics](#)). Mutant *SOD1* protein can misfold and clump inside motor neurons, and lowering it became one of the first goals of a genetic medicine for ALS.

Treatment

There is no cure. NINDS lists **riluzole**, which may reduce glutamate-related damage and extended survival by a few months in trials, and **edaravone**, which slowed functional decline in some people. Care teams also help with breathing, nutrition, speech devices, and mobility. For people with *SOD1* mutations, a drug now targets the cause of their disease (Section 13.11).

13.10 Huntington's Disease

Huntington's disease is an inherited neurodegenerative disease that causes uncontrolled movements, emotional and psychiatric problems, and a decline in thinking ability. The adult form usually begins in a person's 30s or 40s ([MedlinePlus Genetics](#)).

A genetic stutter

Huntington's disease is caused by a change in the *HTT* gene, which makes a protein called **huntingtin**. Inside the gene is a short DNA "word" of three letters, **C-A-G**, repeated many times in a row like a stutter: CAG CAG CAG CAG...

The number of repeats is what matters. MedlinePlus Genetics gives these ranges.

Number of CAG repeats	What it means
10 to 35	Does not cause Huntington's disease (but 27 to 35 repeats can lengthen into the disease range when passed to a child)
36 to 39	May or may not develop Huntington's disease

Number of CAG repeats	What it means
40 or more	Almost always develop Huntington's disease

Too many repeats produce an abnormally long huntingtin protein. It is cut into toxic fragments that clump inside neurons, another example of protein misfolding. The neurons hit hardest are in the **striatum**, part of the basal ganglia ([Chapter 7](#)), which act like a brake on unwanted movements. When striatum neurons die, the brake fails, and the person develops **chorea**: jerky, dance-like movements they can't control. Depression, irritability, and trouble with planning and judgment are also common and can be among the earliest signs.

Inheritance: a coin flip

Huntington's disease is **autosomal dominant**: one altered copy of the gene is enough to cause it. So each child of a parent with Huntington's disease has a 50 percent chance of inheriting the gene variant ([NINDS](#)). The repeat can also grow longer as it passes from one generation to the next. Longer repeats tend to cause earlier symptoms, a pattern called **anticipation**.

A hard question, worth thinking about



This part is heavy. A simple blood test can show whether a healthy 20-year-old carries the Huntington's gene, yet no treatment can stop the disease. Whether to take that test is a very personal choice, which is why genetic counselors help families decide.

Treatment

NINDS states that no treatment can stop or reverse Huntington's disease. Medicines such as tetrabenazine, deutetrabenazine, and valbenazine can reduce chorea, and other medicines help with depression and other psychiatric symptoms. Researchers are testing genetic approaches to lower the harmful huntingtin protein, including experimental gene therapies. In September 2026, the company developing one of them (AMT-130) [asked the](#)

FDA to review it for accelerated approval, but as of October 2026 no gene therapy for Huntington's disease is FDA-approved.

13.11 Fixing the Message: Antisense Drugs and Gene Therapy

Alzheimer's antibodies attack a protein *after* it is made. Some newer medicines act earlier, on the gene's message. Recall the central idea from biology class.

DNA (gene) → mRNA (a working copy of the instructions) → protein

Think of DNA as a cookbook locked in the library (the nucleus). To cook, the cell photocopies one recipe (the mRNA) and carries it to the kitchen (the ribosomes), where the protein is made.

Antisense oligonucleotides: a sticky note on the recipe

An **antisense oligonucleotide (ASO)** is a short, lab-made strand of genetic letters designed to stick to one specific mRNA, the way one half of a zipper fits only its partner. Depending on its design, an ASO can tell the cell to destroy that mRNA, so less of a harmful protein is made. Or it can change how the mRNA is spliced (cut and joined), so more of a useful protein is made. It's like a sticky note on one recipe saying either "don't make this" or "make the full version."

Two ASOs are landmarks in neurology. Both are injected into the fluid around the spinal cord by lumbar puncture (an **intrathecal** injection), so the drug reaches the brain and spinal cord directly.

- **Nusinersen (Spinraza)** treats spinal muscular atrophy (SMA), an inherited disease in which children lose lower motor neurons because they lack enough of a protein called SMN. Nusinersen changes how the mRNA from a backup gene, *SMN2*, is spliced, so the cell makes more full-length SMN protein (Finkel et al., 2017). In December 2016, it became the first FDA-approved drug for SMA, showing that an ASO could change the course of a motor neuron disease.
- **Tofersen (Qalsody)** treats ALS caused by SOD1 mutations. It sticks to SOD1 mRNA and lowers the production of SOD1 protein, including the toxic mutant form (FDA). It was

the first approved treatment aimed at a genetic cause of ALS. Its story, told in the Bedside case below, shows how biomarkers now shape drug approval.

Gene therapy: delivering a new recipe

Gene therapy treats disease by modifying a person's genes. According to the [FDA](#), it can work by replacing a disease-causing gene with a healthy copy, inactivating a gene that is not working properly, or introducing a new or modified gene. One common approach uses a harmless, emptied-out virus as a delivery truck that carries a working copy of a gene into cells.

The first gene therapy for SMA, **onasemnogene abeparvovec (Zolgensma)**, was [approved by the FDA on May 24, 2019](#) for children under 2 years old. A single infusion into a vein delivers a working copy of the human *SMN* gene to motor neurons.

Approach	What it targets	Example	How it's given
Anti-amyloid antibody	A misfolded protein already made	Lecanemab, donanemab (Alzheimer's)	Into a vein (lecanemab also under the skin)
Antisense oligonucleotide	The mRNA message	Nusinersen (SMA), tofersen (SOD1-ALS)	Into spinal fluid, repeated doses
Gene therapy	The gene itself	Onasemnogene abeparvovec (SMA)	One-time infusion into a vein

At the Bedside: Two Patients, Two Misfolded Proteins

 **Meet the patient**

Mr. Okafor is a 74-year-old retired accountant. Over two years, his wife has noticed that he repeats stories, misses appointments, and recently paid the same bill twice. He still drives, dresses himself, and plays chess with his grandson. He says, "My memory isn't what it was, but I'm fine." His wife is worried.

What the doctor checks: The neurologist takes a history from both Mr. Okafor and his wife, because people with memory loss often underestimate it. Blood tests rule out low vitamin B12 and thyroid problems. On a memory test he can't recall a word list after a few minutes, even with hints, but attention and language are mostly normal. An MRI shows mild shrinkage of the hippocampus on both sides and no stroke or tumor. An amyloid PET scan is positive, showing amyloid plaques across the cortex.

Where is the problem? (localization): Trouble *storing* new memories, with older memories and language still working, points to the hippocampus and entorhinal cortex in the medial temporal lobes. The shrinkage on MRI matches. Because he still manages most daily activities, his symptoms fit mild cognitive impairment or the edge of mild dementia, not normal aging.

Diagnosis: Early Alzheimer's disease (mild cognitive impairment due to Alzheimer's disease).

Why it happens: As the biomarker model predicts, beta-amyloid has probably built up for many years. Tau tangles have spread into his memory circuits, synapses have been lost, and hippocampal neurons have died.

Treatment today: His doctor discusses an anti-amyloid antibody, since he is in the early stage these drugs are approved for and his amyloid is confirmed. Before starting, he would have APOE e4 genetic testing and a baseline MRI, then regular MRIs to watch for ARIA. The doctor is honest about the trade-off. In trials, these drugs modestly slowed decline (they did not stop or reverse it), they require regular infusions or injections, and ARIA can rarely be serious. A cholinesterase inhibitor may also help symptoms. Just as important are safety planning (including driving), blood pressure control, exercise, social activity, and caregiver support.

What's new in research: On May 16, 2025, the FDA cleared the [first blood test to help diagnose Alzheimer's disease](#), for adults 55 and older with symptoms. The FDA said this less invasive option could reduce reliance on PET scans and make diagnosis more accessible.

? Your turn: diagnose a variation



A 47-year-old woman has had weakness in her right hand for six months. She now drops her keys and trips on her right foot. Her memory is fine. On exam, the muscles in her hand are thin and twitch under the skin, yet her reflexes are unusually brisk. Her father and an aunt both died of a "muscle disease" in their 50s. What do you suspect, and what new treatment might her doctors discuss?

Answer: Weakness, muscle wasting, and twitching (lower motor neuron signs) together with brisk reflexes (upper motor neuron signs), plus a family history, suggest **familial ALS**. Genetic testing could look for a *SOD1* mutation. If one is found, doctors may discuss **tofersen (Qalsody)**. It received **FDA accelerated approval on April 25, 2023**, based on its ability to lower **neurofilament light** in blood. Neurofilament light is a blood biomarker of axon injury and neurodegeneration. Accelerated approval is an FDA pathway for serious diseases when a drug improves a biomarker "reasonably likely" to predict real benefit. Continued approval may depend on trials confirming that benefit.

Be honest about the evidence: in the phase 3 VALOR trial, tofersen lowered SOD1 and neurofilament light, but it **did not meet its primary clinical endpoint**, the change in a function rating scale at 28 weeks (Miller et al., 2022). A 52-week follow-up hinted that starting earlier was better, but that was not the trial's main test. A confirmatory trial (ATLAS) is testing whether tofersen delays symptoms in SOD1 carriers who are still healthy. As of October 2026, it is still under way and has not reported results. Tofersen is given by lumbar puncture, and procedure-related side effects are common.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Dementia is a normal part of getting old.

Reality: Some slowing of memory and thinking is normal with age, but dementia is not. Dementia is caused by diseases that damage the brain, and many people live into their 90s and beyond without it.

Myth: There are no treatments at all for Alzheimer's disease.

Reality: Several medicines help with symptoms, and two anti-amyloid antibodies (lecanemab and donanemab) are FDA-approved for early-stage disease. They modestly slow decline but do not cure the disease.

Myth: Removing amyloid plaques will bring back lost memories.

Reality: By the time symptoms appear, tau has spread and many neurons have died.

Neurons that have died are not replaced, so clearing amyloid can slow decline but cannot restore what was lost.

Myth: If you carry the APOE e4 gene, you will definitely get Alzheimer's disease.

Reality: APOE e4 raises risk but doesn't decide anyone's fate. Many carriers never develop the disease, and many people with Alzheimer's disease don't carry it. Huntington's disease is different: with 40 or more CAG repeats, a person almost always develops it.

Brain Bee Practice

? 1. Name the two abnormal protein deposits that define Alzheimer's disease, and say where each is found. ✓

Amyloid plaques, made of beta-amyloid, are found outside neurons. Neurofibrillary (tau) tangles, made of abnormal tau, are found inside neurons.

? 2. Which two brain structures does Alzheimer's disease usually damage first, and what symptom does that explain? ✓

The entorhinal cortex and the hippocampus. Damage there explains early trouble forming new memories.

? 3. What type of neurons die in ALS, and what are two signs of damage to each type? ✓

Motor neurons. Lower motor neuron damage causes weakness, muscle wasting, and twitching (fasciculations). Upper motor neuron damage causes stiffness (spasticity) and brisk reflexes.

? 4. What genetic change causes Huntington's disease, and what are the chances that a child of an affected parent inherits it? ✓

An expanded CAG repeat in the *HTT* (huntingtin) gene. It is autosomal dominant, so each child has a 50 percent chance of inheriting it.

 5. What is an antisense oligonucleotide? Name one approved for a neurological disease.

A short, synthetic strand of genetic material that binds a specific mRNA to reduce or change production of a protein. Examples: nusinersen for spinal muscular atrophy, or tofersen for SOD1-ALS.

Exercises

Remember

1. Define *neurodegeneration* in your own words.

 Answer

Neurodegeneration is the progressive loss of the structure and function of neurons, ending in their death.

2. What is ARIA, and how do doctors check for it?

 Answer

ARIA (amyloid-related imaging abnormalities) is temporary brain swelling, sometimes with small spots of bleeding, that can happen with anti-amyloid antibodies. Doctors check for it with regular MRI scans.

Understand

1. Explain why trouble forming new memories is often the first sign of Alzheimer's disease.

 Answer

Alzheimer's damage usually begins in the entorhinal cortex and hippocampus, the structures that turn new experiences into lasting memories. Older memories stored elsewhere in the cortex are affected later.

2. Explain the difference between a *biomarker* and a *symptom*, using Alzheimer's disease as an example.

 Answer



A symptom is something the person or family notices, such as forgetting appointments. A biomarker is something measured in the body, such as amyloid on a PET scan or in blood. Biomarkers can become abnormal years before symptoms appear.

Apply

1. A 30-year-old's mother has Huntington's disease. His genetic test shows 42 CAG repeats in one copy of *HTT*. Using the table in Section 13.10, what does this result mean for him, and what is the chance that each of his future children inherits the expanded gene?
2. Use the Amyloid and Tau Cascade MicroSim. Find the age at which each curve first crosses the "abnormal on tests" line, and calculate how many years pass between amyloid becoming abnormal and symptoms becoming abnormal in this schematic model.

Analyze

1. Compare an anti-amyloid antibody, an antisense oligonucleotide, and gene therapy. For each, identify the step in the DNA → mRNA → protein pathway it acts on and why that step fits the disease it treats.
2. Two 80-year-olds have similar amyloid on PET scans. One has dementia; the other manages her own money and plays bridge. Use cognitive reserve and the biomarker model to analyze possible reasons.

Evaluate

1. Tofersen received accelerated approval because it lowered neurofilament light, although its phase 3 trial missed its primary clinical endpoint. Is approving drugs based

on biomarkers a good idea for rare, fatal diseases? Defend your answer, weighing patients' urgent need against the risk of approving a drug that doesn't help.

2. A news headline says: "New Alzheimer's drug stops memory loss." Using what you know about the lecanemab and donanemab trials, judge how accurate this headline is and rewrite it to be accurate.

Create

1. Design a one-page family handout that separates normal forgetfulness from warning signs of dementia. Include four comparisons and one reason to see a doctor even if it seems like "just age."
2. Design a trial testing whether an anti-amyloid antibody delays symptoms when started in the preclinical stage. Say who you would enroll, which biomarker you'd use to choose them, your main outcome, and how you'd watch for ARIA.

Key Takeaways

- Normal aging brings slower thinking and some shrinkage, but not large-scale neuron loss. **Dementia is not a normal part of aging.**
- Many neurodegenerative diseases share one theme: a **misfolded protein** builds up in specific neurons, and the location decides the symptoms.
- **Alzheimer's disease**, the most common cause of dementia, is defined by **amyloid plaques** outside neurons and **tau tangles** inside them. It usually starts in the hippocampus and entorhinal cortex.
- **Biomarkers** (PET scans, spinal fluid, and now FDA-cleared blood tests) show that Alzheimer's brain changes begin a decade or more before symptoms.
- **Anti-amyloid antibodies** (lecanemab and donanemab) are FDA-approved for early Alzheimer's disease. They modestly slow decline, are not cures, and carry a risk of **ARIA**.
- **ALS** kills upper and lower motor neurons. **Huntington's disease** comes from an expanded CAG repeat in *HTT*, is autosomal dominant, and damages the striatum.

- **Antisense oligonucleotides** (nusinersen, tofersen) and **gene therapy** target genes and their messages. Tofersen's accelerated approval rested on a biomarker; its phase 3 trial missed its main clinical goal.

You made it through a tough chapter!



You can now explain plaques, tangles, CAG repeats, and antisense drugs, the vocabulary behind some of the newest work in medicine. Next, in Chapter 14, we look at damage that happens in seconds instead of decades: concussion, stroke, and seizures.