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Memory – III. The Neurodegenerated Brain

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Abstract

In this Article, I dwell on the diseased brain especially in the case of neurodegenerative diseases such as more particularly dementia and Alzheimer's disease. With increasing lifespan in the developed world, dementia has become an increasing public health concern. Whilst uncommon in pre-industrial times and relatively rare before the 20th century, as more people are living longer, dementia is becoming more common in the population as a whole due to a decrease in risk factors.

The disease remains one of the most misunderstood diseases in medicine. After defining it and its several types, I set forth their various particulars, including the affected brain areas and their deleterious effects on memory. I will also conduct a similar analysis and abundantly illustrate with neuroradiological images of different types the case of the Alzheimer's diseased brain.

For some of the important other neurodegenerative diseases (Parkinson's disease, multiple sclerosis, multiple system atrophy, Tourette's syndrome and also epilepsy), appropriate references are provided.

Abbreviations

AD: Alexander's disease; AD: Alzheimer's disease; ADD: AD dementia; ADL: Adenoleukodystrophy; BD: Behcet's disease; CAT: Computerized axial tomography; CBD: Corticobasal degeneration; CD: Celiac disease; CD: Children's dementia; CD: Cortical dementia; CID: Chronic inflammatory disease; CJD: Creutzfeldt-Jacob disease; CJDD: CJD dementia; CSH: Chronic subdural hematoma; CT: Computed tomography; CTE: Chronic traumatic encephalopathy; CV: Cerebral vasculitis; CX: Cerebrotendinous xanthomatosis; DLB: Dementia with Lewy bodies; DPA: Dentatorubal pallidoluysian atrophy; FFI: Fatal familial insomnia; fCA: Frontal cortical atrophy; fMRI: funtional MRI; FTD: Frontotemporal disorders; FXTAS: Fragile X-associated tremor/ataxia syndrome; GA: Glutaric aciduria; GD: Gaucher's disease; HAD: HIV-associated dementia; HD: Huntington's disease; HDD: HD dementia; HE; Hashimoto's encephalopathy; IMD: Immunologically-mediated

dementia; KD: Krabbe's disease; LB: Lewy bodies; LBD: LB dementia; LD: Lyme disease; LE: Limbic encephalitis; MCLD: Metachromatic leukodystrophy; MD: Mixed dementia; MID: Multi-infarct dementia; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; MS: Multiple Sclerosis; MSA: Multiple system atrophy; MSUD: Maple syrup urine disease; MTLA: Medial temporal lobe atrophy; NCL: Neuronal ceroid lipofuscinosis; NDD: Neurodegenerative diseases; NDDD: NDD dementia; NFT: neurofibrillary (tau) tangles; NPD: Niemann-Pick disease; NPH: Normal pressure hydrocephalus; PA: Posterior atrophy; PD: Parkinson's disease; PD: Primary dementia; PD: Pugilistic dementia; PDD: Parkinson's disease dementia; PET: Positron emission tomography; PID: Progressively irreversible dementia; PKAN: Panthotenate kinase-associated neurodegeneration; PMD: Pelizaeus-Merzbacher disease; PSP: Progressive supranuclear palsy; RD: Reversible dementia; REM: Rapid eye movements; RSD: Reversible secondary dementia; SASE: sub-acute sclerosing encephalitis; SCA: Spinocerebellar ataxia; SCD: SubCD; SD: Senility dementia; SFS: San Filippo's syndrome; SLE: Systemic lupus errhythematosus; SPECT: Single photon emission computerized tomography; SS: Sjogren's syndrome; SyD: Syphilitic dementia; TS: Tourette's syndrome; TSD: Tay-Sachs disease; VD: Vascular disease; VDD: VD dementia; VE: Viral encephalitis; WD: Wilson's disease; WD: Whipple's disease; WHO: World Health Organization; YOD: Young onset dementia.

Keywords

Alzheimer's diseased brain; Demented brain; Dementia; Memory; Neurodegenerated brain.

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Articles I and II in this series related to memory in the healthy and aging brain, respectively. Here, I will dwell on memory in the diseased brain, particularly in the case of neurodegenerative diseases such as essentially dementia and Alzheimer's disease (AD). other such diseases as Parkinson's disease (PD), multiple sclerosis (MS), multiple system atrophy (MSA), Lyme disease (LD), Tourette's syndrome (TS), and even epilepsy will not be included here but appropriate references to my own publications will be provided.

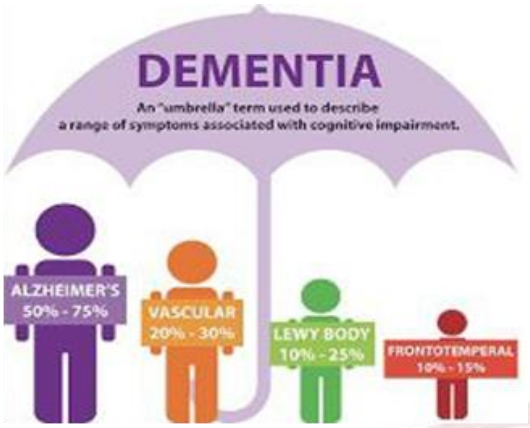
With increasing lifespan in the developed world, dementia and its deleterious effects on memory have become an increasing public health concern. Whilst uncommon in pre-industrial times and relatively rare before the 20th century, as more people are living longer, dementia is becoming more common in the population as a whole due to a decrease in risk factors.

The World Health Organization (WHO) characterizes dementia as "...one of the greatest health challenges of our generation" and the "...7th leading cause of death globally, account(ing) for less than 1.5% of total health research output."

Accordingly, that organization set forth a "Global action plan on the public health response to dementia 2017-25" as well as a "blueprint for dementia research". In 2016, Alzheimer's and other dementia types costed annually $ 818 billion (excluding the majority of care that is provided by family carers), the cost of care having increased since that time. This article will rather focus on the deleterious effects on memory.

The demented brain

Dementia is an umbrella term for several brain diseases that manifest themselves by a group of symptoms affecting memory, other cognitive abilities, and behaviour.



(Note: The umbrella shown is not wide enough as there are several other conditions that should also be included under it.)

Figure 1: Dementia is an umbrella term for several different conditions

But dementia is not an emerging disease! It has been referred to in medical texts since Antiquity (see the writings of Pythagoras, Solon, Plato, Cicero, Celsius, Galen, Bacon,...and others in Asia and China) although the disease was comparatively rare before the 20th century. Until the end of the 19th century, it was a much broader clinical concept that encompassed mental illness and any type of psychosocial incapacity. In the elderly, it was also believed to be the result of blockages of the major arteries supplying the brain or small strokes within the vessels of the cerebral cortex (two forms of cerebral atherosclerosis). It was only recently, on the basis of pathological examination of brain tissues, symptomatology, and different patterns of brain metabolic activity that a number of other types of dementia have been identified.

After all these past centuries, dementia remained (and continues to be) one of the most misunderstood diseases in medicine. It is only in the 1960s that the link between age-related cognitive decline and neurodegenerative diseases (NDD) was established. Since then, the medical community maintained that AD was the cause of the vast majority of mental impairments rather than vascular disease (VD), which is rarer than previously thought. It also thought that senility dementia (SD) could be linked to AD dementia (ADD), and that dementia is a mixture of both ADD and VD dementia (VDD). Since the beginning of the current century, a number of other types of dementia have been differentiated from these two.

Nonetheless, to this day, the causal etiology of many types of dementia, including ADD, still remains unclear. While many theories (rather hypotheses) have been advanced, these are largely based on risk factors, associations or correlations. But, risk factors, correlations, associations, and the like... are not causation! Likewise, risk management and symptomatic treatment... are not cure, only palliation! More recently (Fymat, 2017), I have posited that the root cause (not a risk factor) of Alzheimer's and other neurodegenerative diseases is but a "*runaway autoimmune disease*" and further charted a path to its cure (Fymat 2020a, b).

What is dementia?

Simply stated, dementia is a general term for the process of decline in mental abilities. According to the definition provided by the WHO (2017), dementia is *"...an umbrella term for several diseases affecting memory, other cognitive abilities, and behavior that interfere significantly with a person's ability to maintain their activities of daily living. Although age is the strongest known risk factor for dementia, it is not a normal part of aging".* It is thus a broad category of brain diseases that cause a long-term and often gradual decrease in the ability to think and remember that is great enough to affect a person's daily functioning. Other common symptoms include emotional problems, language difficulties, and decreased motivation.

As pictured in part in Figure 1, many different diseases can cause dementia, including AD, VD, Lewy bodies (LB), frontotemporal disorders (FTD), syphilis, senility,

and even stroke. Mixed dementia (MD) is the concurrence of two or more types of dementia. About 10% of individuals present with MD, usually the combination of AD and another type of dementia such as FTD or VD.

However, not being a specific disease, the above potential contributors do not reach to the primary cause of the disease. There lies our greatest shortcoming: Unable to pinpoint the root cause of the disease, we are powerless in curing it. Sure, drugs are available to treat some of the symptoms, but not the disease itself. They may improve symptoms or at best slow down the disease but there is no known cure for dementia. This is a sad observation on the current state of the situation, which stems from our incomplete understanding of the deep biology of the contributing diseases and associated epigenetic/ecogenetic influences.

Risk factors and prevention

Although age is the strongest known risk factor for dementia, it is not an inevitable consequence of aging (see **Table 1**).

Age	Contributor(s)	Treatment effects
< 40	o Rare without other neurological disease o Genetic disorders can cause true neurodegenerative disease dementia (NDDD): - Alzheimer's disease dementia (ADD) - Spinocerebellar ataxia (SCA) type 17 dominant inheritance - X-linked adenoleukodystrophy (ADL) - Gaucher's disease (GD) type 3 - Metachromatic leukodystrophy (MCLD) - Niemann-Pick disease (NPD) - Panthotenate kinase-associated neurodegeneration (PKAN) - Tay-Sachs disease (TSD) - Wilson's disease (WD)	o Treatment of underlying psychiatric illness, alcohol, drug abuse, or metabolic disturbance
< 65	o ADD is most frequent. Inherited forms account for higher proportion o Frontotemporal lobar degeneration (FTLD) o Huntington's disease (HD) accounts for the rest o Vascular disease dementia (VDD) in cases of repeated brain traumas o Chronic traumatic encephalopathy (CTE)	
> 65	o ADD o VDD o Dementia with Lewy bodies (DLB) occurring alongside either ADD or/and VDD o Hypothyroidism o Normal pressure hydrocephalus (NPH)	o Fully reversible with treatment o Treatment may prevent progression and improve other symptoms

Source: Fymat A. L., 2017 – 2020

Table 1: Dementia variations with age of occurrence

Further, dementia does not exclusively affect older people – young onset dementia (YOD), defined as the onset of symptoms before the age of 65 years, accounts for up to 9% of cases. Some research has shown a relationship between the development of cognitive impairment and lifestyle-related risk factors that are shared with other noncommunicable diseases. These risk factors include:

- Clinical conditions: Diabetes, depression, midlife hypertension, and obesity.
- Lifestyle habits: Unhealthy diets, physical inactivity, tobacco use, and harmful use of alcohol.
- Educational and social limitations: Low educational attainment, social isolation, and cognitive inactivity.

Signs and symptoms

Most dementia types are slow and progressive. Symptoms vary across types and stages and also with the individual. A diagnosis requires a change from a person's usual mental functioning and a greater decline than one would expect due to aging. The signs and symptoms evolve in three consecutive phases (early, middle, and late phase) ending up in near total dependence and inactivity, serious memory disturbances, and more obvious physical signs and symptoms.

Behavioral and psychological symptoms of dementia occur almost always in all types of dementia and may manifest as agitation/aggression, anxiety, apathy, appetite changes, behavioral changes, delusions/ hallucinations, depression, disinhibition, impulsivity, irritability, mood elations, motor abnormalities, psychosis, and sleep disturbances.

Each form of dementia has its own risk factors, but most forms have several risk factors in common (se also above). It is not known how treatment for these problems influences the risk of developing dementia. It seems as though people who remain physically active, socially connected, and mentally engaged are less likely to fall prey to dementia (or develop dementia later) than others. To compound things, more than one type of dementia may exist in the same person.

Dementias according to the affected brain areas

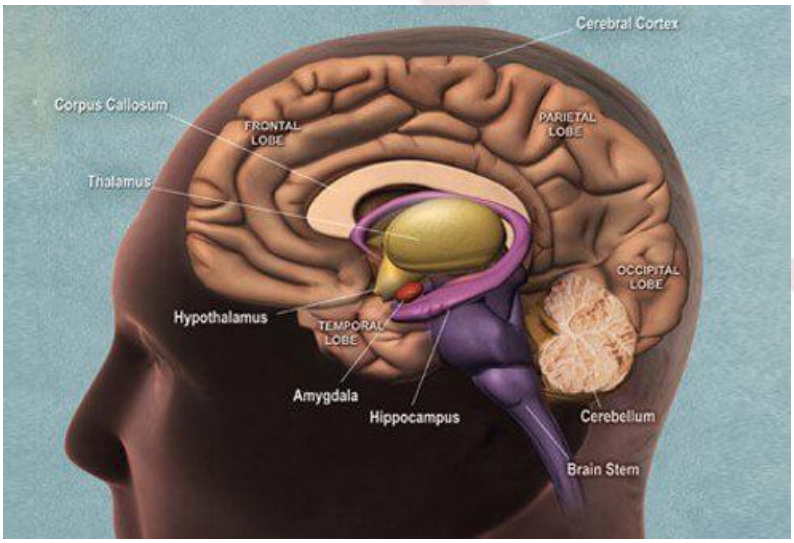


Figure 2: Brain areas affected by dementia

Figure 2 is a pictorial representation of the affected brain regions, as presented below, inducing the effects caused therein:

- **Cortex:** Thought; perception and language; emotions and behavior. It devolves into three subcategories:
  - **Cortical:** Memory (severe loss), language;
  - **Subcortical:** Ability to start activities, speed of thinking; and
  - **Corticobasal degeneration. Hippocampus:** Memory.
- **Midbrain and substantia nigra:** Movement.
- **Brainstem:** Sleep, alertness, and autonomic dysfunction.
- **Hypothalamus:** Autonomic dysfunction.
- **Olfactory cortex:** Smell.

Also affected are the:

- **Spinal cord and peripheral nervous system:** Autonomic dysfunction.

Let me briefly summarize these dementia types:

Cortical dementia (CD)

Cortical dementia (CD) occurs because of problems in the cerebral cortex, the outer layer of the brain. This type of dementia plays an important role in memory and language. People with CD usually have severe memory loss and cannot remember words or understand language.

Subcortical dementia (SCD)

Subcortical dementia (SCD) occurs because of problems in the part of the brain beneath the cortex. It affects the individual's ability to start activities and speed of thinking. Forgetfulness and language problems are typically not developed. Examples are Parkinson's disease dementia (PDD), Huntington's disease dementia (HDD), and HIV-associated dementia (HAD).

Corticobasal degeneration (CBD)

Corticobasal dementia (CBD) is a rare form of dementia characterized by many different types of neurological problems that get progressively worse over time. The affected brain area is the posterior frontal lobe and parietal lobe, although many other brain parts can be affected.

It is a loss of nerve cells (atrophy) in the cerebral cortex and the basal ganglia areas of the brain. A corresponding illustrative brain is shown in Figure 2. It shares similar symptoms as ADD - memory loss, speech difficulty, and trouble swallowing.

Category	Characteristics	Symptoms	Disease examples
Affected brain area	Cortical (outer cortex)	o Memory o Thinking (thought, perception) o Language o Social behavior	o Alzheimer's disease dementia (ADD) o Creutzfeldt-Jacob disease dementia (CJDD) o Dementia
	Subcortical (below the cortex)	o Memory (speed of thinking) o Emotions o Movement (ability to start	o Parkinson's disease dementia (PDD) o Huntington's disease dementia (HDD)

		activities)	o HIV-associated dementia (HAD)
	Corticobasal	o Many types of neurological problems	o ADD o PDD o Parkinsonism o CJDD
	Hippocampus	o Memory	o ADD
	Midbrain and substantia nigra	o Movement	o PDD
	Brain stem	o Speed o Alertness o Autonomic dysfunction	o PDD
	Hypothalamus	o Autonomic dysfunction	o PDD
	Olfactory cortex	o Smell	o ADD
Progressive, irreversible	Becomes worse over time	o Interference with more and more cognitive abilities	o ADD o Lewy body dementias (LBD) o Vascular disease dementia (VDD) o Multi-infarct dementia (MID) o Frontotemporal disease dementia (FTDD) o Mixed dementia (MD)
Secondary to another disorder	Primary (does not result from any another disease)	o Dementia	o ADD
	o Secondary (peripheral to a pre-existing mental illness or condition, or injury) o The different symptoms depend on the seats of the lesions	o Brain infections o Multiple sclerosis (MS) o Some degree of paralysis, tremor, nystagmus, and speech disturbances. o Heterogeneous deterioration with nuchal dystonia and dementia	o Brain infections o Progressive supranuclear palsy (PSP) o Multiple sclerosis (MS)

Source: Fymat A. L., 2017 - 2020

Table 2: Categorization of dementia types

Table 2 is a categorization of the several dementia types, including their characteristics, symptoms, and disease examples.

As seen, Alzheimer's disease dementia (ADD) occupies a special place as it originates in the cortex, is progressive and irreversible, and is a primary dementia. It also occurs in the corticobasal area, the hippocampus, and the olfactory cortex.

Creutzfeldt-Jakob disease dementia (CJDD) also takes place in the cortex and the corticobasal area whereas Parkinson's disease dementia (PDD) and features of parkinsonism (poor coordination, muscle rigidity, and shaking) occur in the subcortical area, the corticobasal area, the midbrain, the substantia nigra, the brain stem, and the hypothalamus.

Signs are difficulty using only one limb (named "alien limb") over which there seems to be no brain control, asymmetric symptoms including jerky movements of one or more limbs (myoclonus), strange repetitive movements (dystonia), speech difficulty (inability to move mouth muscles in a coordinated way), numbness and tingling of the limbs, and neglect of one side of the vision or senses. In neglect, a person ignores the opposite

side of the body from the one that has the problem.

Patients with CBD deteriorate to the point where they can no longer care for themselves, and often die from secondary medical issues such as pneumonia or severe infection (sepsis).

Reversible and progressively irreversible dementias

Reversible dementias (RD)

There are four main causes of easily reversible dementia:

- **Hypothyroidism;**
- **Vitamin B12 deficiency;**
- **Lyme disease (LD);** and
- **Neurosyphilis.**

All people with memory difficulty should be checked for hypothyroidism and B12 deficiency. For Lyme disease (LD) – see the references at the end of this Article - and neurosyphilis, testing should be done if there are risk factors for those diseases. Because risk factors are often difficult to determine, testing for LD and neurosyphilis, as well as other unmentioned factors, may be undertaken as a matter of course in cases where dementia is suspected.

Progressively irreversible dementias (PIDs)

Neurodegenerative disorders result in a progressive and irreversible loss of neurons and brain functioning. These progressively irreversible dementias (PIDs) become worse over time and patients eventually lose more of their abilities. Currently, there are no cures for these types of disorders. They include:

- Alzheimer's disease dementia (ADD);
- Vascular disease dementia (VDD);
- Multi-infarct dementia (MID);
- Lewy body dementias (LBD) including dementia with Lewy bodies (DLB);
- Frontotemporal disorders dementia (FTDD); and
- Mixed dementia (MD): A combination of two or more forms of dementia, at least one of which being ADD. In this context, "pure" dementia is ADD alone.

Dementia secondary to another disorder

This category includes both primary and secondary dementias.

Primary dementia (PD)

Primary dementia (PD) patients only show symptoms of dementia. ADD is a form of primary dementia, which accounts for 50%-75% of all dementia cases.

Reversible secondary dementia (RSD)

A secondary dementia is a form of dementia that develops as a peripheral condition to a pre-existing mental illness or condition. Brain infections, progressive supranuclear palsy (PSP), and multiple sclerosis (MS), whether disseminated, local or insular, are examples of such conditions. Unlike other types of dementias, many types of secondary dementias can be stopped or reversed.

Encephalopathy

Encephalopathy may develop relatively slowly and resemble dementia. Possible causes include:

- Brain infection: Viral encephalitis (VE); sub-acute sclerosing encephalitis (SASE); Whipple's disease (WD); or
- Brain inflammation: Limbic encephalitis (LE); Hashimoto's encephalopathy (HE); cerebral vasculitis (CV); tumors (lymphoma, glioma); drug toxicity (e.g., anticonvulsant drugs);

metabolic causes (liver failure or kidney failure); and chronic subdural hematoma (CSH).

A preliminary look at the principal and common types of dementia

I have charted in Table 3 the principal types of dementia, their causes (or hallmarks), and their symptoms:

Types	Cause(s) or hallmark(s)	Symptoms
Alzheimer's disease dementia (ADD) (most common)	o Amyloid-beta plaques o Neurofibrillary-tau tangles o Loss of connections between neurons	o Memory loss o Severe cognitive deficits
Fronto-temporal disorders dementia (FTDD) (6 types)	o Progressive neuronal loss o Manifests in late adulthood (age 45-65 years) o Equally affecting men and women	o Changes in personal and social behavioral o Apathy o Blunting of emotions o Deficits in both expressive and receptive language) o Memory problems o Difficulty speaking
Lewy body dementia (LBD) including dementia with Lewy bodies (DLB) (much less common than ADD, comparable to VDD, but second to ADD in importance)	o Abnormal deposits of alpha-synuclein protein in the brain	o Impaired cognition o Delusions o Visual hallucinations o Sleep disorders, rapid eye movements (REM) o Behavioral disturbances
Mixed dementia (MD)	o Combination of 2 or more types of dementia, one of which is usually ADD	o Symptoms corresponding to those of the component dementias
Vascular disease dementia (VDD) (may overlap with ADD)	o Reduced blood flow to the brain	o Multiple small strokes

Source: Fymat A. L., Tellwell Talent Publishers 2017 - 2020

Table 3: The principal types of dementia

The main contributors to dementia are summarized in Table 4. Symptoms are very similar in all types of dementia and, thus, cannot by themselves help in reaching the correct diagnosis of demential type(s). At present, the main contributors to dementia are Alzheimer's disease dementia (ADD: 50%-75% of cases), vascular disease dementia (VDD: 25%), Lewy body dementias (LBD: 15%), others of unspecified contribution including Parkinson's disease dementia (PDD), frontotemporal disorders dementia (FTDD), and still others: mixed, senilitic, syphilitic, progressive supranuclear palsy (PSNP), corticobasal degeneration (CBD), encephalopathy, and Creutzfeldt-Jakob disease dementia (CJDD). (see Table 3.) Immunologically mediated, chronic inflammatory conditions include Behcet's disease (BD), multiple sclerosis (MS), sarcoidosis, Sjogren's syndrome (SS), systemic lupus errhythematosus (SLE), and celiac and non-celiac diseases. There are still many other medical and neurological conditions in which dementia only occurs late in the illness.

Disease	Contribution	Characteristics & Symptoms
Alzheimer's disease dementia (ADD)	50% - 75%	CAUSES: o Runaway autoimmune disease (Fymat, 2017) SYMPTOMS: o Short-term memory loss o Repetitions o Getting lost o Difficulties keeping track of bills o Forgetting to take medications o Difficulties finding words o Trouble with visuo-spatial areas o Troubles with reasoning o Troubles with judgment o Troubles with insight SIGNS: o Death of nerve cells (neurons) in important parts of the brain o Hippocampus o Shrinkage of fronto-temporal parts
Vascular disease dementia (VDD)	20% - 30%	CAUSES: o Strokes o Blood vessels diseases o Hypertension o CVDs (particularly previous heart attacks, angina) o Diabetes SYMPTOMS: o Minor strokes SIGNS: o Lost or damaged ischemic brain areas
Dementia with Lewy bodies (DLB)	10% - 20%	CAUSES: o Abnormal protein structures within brain cells o Treatable with medication(s) SYMPTOMS: o PD (trembling, stiffness, slowness) o Visual hallucinations o Difficulties with visuo-spatial functions o Problems with attention, organization, executive functions o Parkinsonism (tremor, rigid muscles, stiffness, slowness, emotionless face, etc. SIGNS: o Vivid long-lasting hallucinations o "Act-out dreams" o Occipital hypoperfusion o Hypometabolism
Frontotemporal disorders dementia (FTDD)	10% - 15%	SYMPTOMS: o Memory problems (not a main feature) o Personality changes o Abnormal social behavior o Language difficulties SIGNS: o Nerve cell loss in frontal and temporal lobes (arise at earlier ages than AD) o Three types: Behavioral, temporal (or semantic), progressive non-fluent aphasia
Mixed dementia (MD)	10%	CAUSE: o More than one (often AD and vascular) SIGNS:

		o Over 80-years of age
Parkinson's disease dementia (PDD)	Unspecified	CAUSE: o During the course of PD SYMPTOMS: o Very similar to PD
Progressive supranuclear palsy (PSP)	Unspecified	SYMPTOMS: o Eye movement problems o Movement problems: Balance problems, falling backwards, slow movements, rigid muscles o Behavioral problems: Irritability, apathy, social withdrawal, depression, progressive difficulty eating and swallowing, eventually talking o Misdiagnosed as PD SIGNS: o Atrophied mid-brain
Corticobasal degeneration (CBD)	Unspecified	SYMPTOMS: o Many different types of neurological problems, getting worse over time SIGNS: o Affected temporal lobes o Difficulty using only one limb (“alien” limb) o Numbness and tingling of limbs o Asymmetric symptoms (myoclonus or jerking movements of one pr more limbs) o Strange repetitive movements (dystonia) o Speech difficulties (inability to move mouth muscles in coordinated way) o Neglect one side of vision or senses
Creutzfeldt-Jakob disease (CJD)	Unspecified	CAUSE: o Prions SYMPTOMS: o Slow, at times rapid, progression
Encephalopathy	Unspecified	CAUSES: o Brain infection: Viral or sclerosing encephalitis and Whipple's disease (WD) o Brain inflammation: Limbic encephalitis (LE), Hashimoto's encephalitis (HE), cerebral vasculitis (CV) o Tumors: Lymphoma, glioma o Drug toxicity (anticonvulsants) o Metabolic causes: liver or kidney failure, chronic subdural hematoma (CSH)
Senility dementia (SeD)	Unspecified	
Normal pressure hydrocephalus (NPH)	Unspecified	
Syphilitic dementia (SyD)	Unspecified	
Immunologically-mediated dementia (IMD)	Unspecified	CAUSES: o Chronic inflammatory conditions (CID) o Behcet's disease (BD) o Multiple sclerosis (MS) o Sarcoidosis o Sjogren's syndrome (SJ) o Systemic lupus errhythematosus (SLE) o Celiac disease (CD) o Non-gluten celiac sensitivity SIGNS: o Can rapidly progress o Good response to early treatments (immunomodulators, steroids)
Inherited conditions	Unspecified	CAUSES: o Alexander's disease (AD) o Cerebrotendinous xanthomatosis (CX)

		o Dentatorubal pallidoluysian atrophy (DPA) o Epilepsy o Fatal familial insomnia (FFI) o Fragile X-associated tremor/ataxia syndrome (FXTAS) o Glutaric aciduria (GA) type 1 o Krabbe's disease (KD) o Maple syrup urine disease (MSUD) o Niemann-Pick disease (NPD) type C o Neuroacanthocytosis o Neuronal ceroid lupofuscinosis (NCL) o Organic acidemias o Pelizaeus-Merzbacher disease (PMD) o San Filippo's syndrome (SFS) type B o Spinocerebellar ataxia (SCA) type 2 o Urea cycle disorders
Other conditions including: o Pugilistic dementia (PD) o Children's dementia (CD)	Unspecified	CAUSES: o Cumulative damage in the brain (e.g., in chronic alcoholism, repeated head injuries, etc. o Dementia in children

Source: Fymat A. L., 2017 -2020

Table 4: Contributors to dementia

Inherited conditions include various pathologies:

- Diseases: Alexander's (AD), Krabbe's (KD), Niemann-Pick (NPD) type C, maple syrup urine (MSUD), Pelizaeus-Merzbacher (PMD), and epilepsy.
- Syndromes: Fragile X -associated tremor/ataxia and San Filippo's syndrome (SDS) type B.
- Other disorders: Cerebrotendinous xanthomatosis (CX), dentatorubal pallidoluysian atrophy DPA), fatal familial insomnia (FFI), glutaric aciduria (GA) type 1, neuronal ceroid lipofuscinosis (NCL), neuroacanthocytosis, organic acidemias, spinocerebellar ataxia (SCA) type 2, and urea cycle.

As indicated earlier, there are, nonetheless, some reversible conditions such as hypothyroidism, Vitamin B12 deficiency, Lyme disease, and neurosyphilis. Except for the treatable types of dementia listed above, and in the absence of a thorough understanding of the deep biology of this disease, there is currently no cure. Medical interventions remain heretofore palliative in nature with aim to alleviate pain and suffering. Other minor contributors are also mentioned later in this section.

The Alzheimer-diseased brain

While we continue to unravel the complex brain changes involved in the onset and progression of AD, it seems likely that damage to the brain started a decade or more before memory and other cognitive problems appeared. During this preclinical stage of AD, people seem to be symptom-free but toxic changes are taking place in the brain. Abnormal deposits of proteins form amyloid plaques and intra-neural neurofibrillary (tau) tangles (NFT) throughout the brain and, once-healthy neurons stop functioning, they lose connections with other neurons and die.

Molecular and cellular changes in AD

Many molecular and cellular changes take place in the brain of a person with AD. These changes can be observed in brain tissue under the microscope after death. The damage initially appears to take place in the hippocampus, that part of the brain that is essential in forming memories. As more neurons die, additional parts of the brain are affected, and they begin to shrink.

By the final stages of AD, damage is widespread and brain tissue has shrunk significantly. Investigations are underway to determine which changes may cause AD and which may be a result of the disease.

Neuroradiological imaging

In Figure 3, I contrast a healthy brain (left side) with a severe Alzheimer-diseased one (right side). It is readily seen that the brain structure and convolutions are distorted with extreme shrinkage of the cerebral cortex and the hippocampus, and ventricles are severely enlarged. In fact, the extent of brain shrinkage is an indicator and a rough gauge for assessing the severity of the disease.

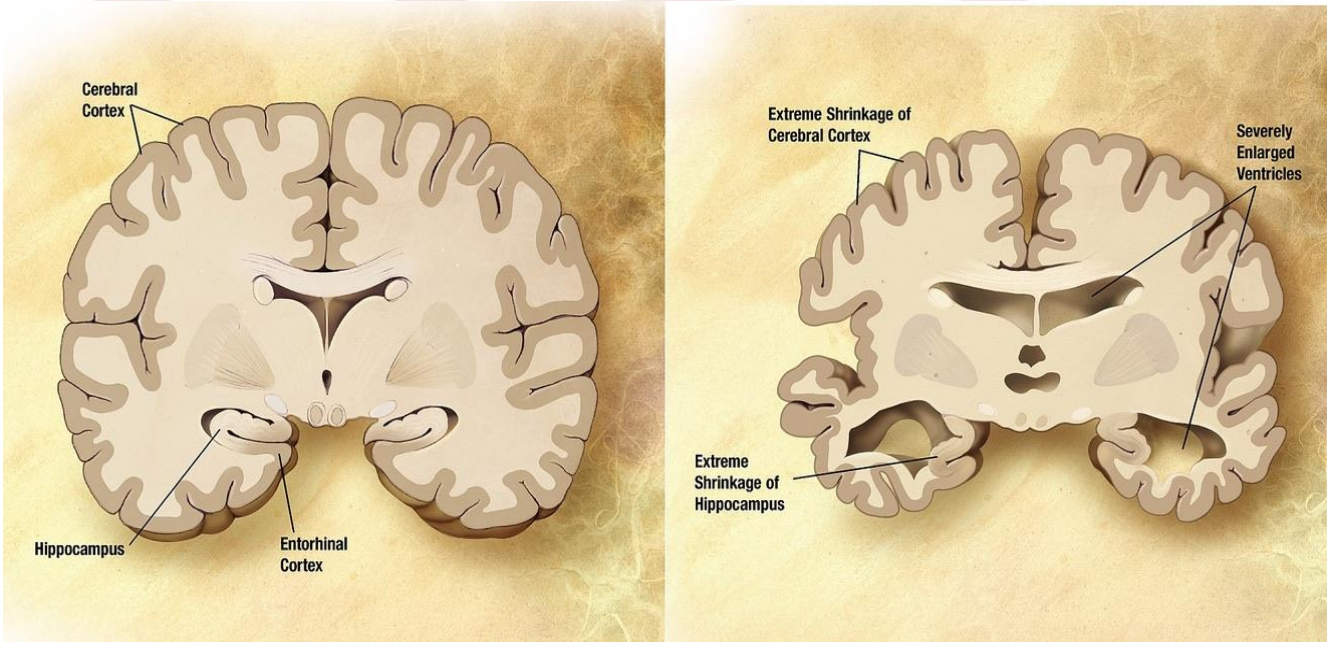


Figure 3: Contrasting a healthy brain with a severe Alzheimer-diseased brain

The brain ravages are further accentuated in Figure 4 where the shrinkage is highlighted (blue color) from preclinical AD to mild-to-moderate AD to severe AD. The anatomical pictures in Figures 3 and 4 can be better seen with different radiological imaging apparatuses. Such apparatuses include computerized tomography (CT) or computerized axial tomography (CAT); single photon emission computerized tomography (SPECT); magnetic resonance imaging (MRI) and its variants functional MRI (fMRI), magnetic resonance angiography (MRA) and magnetic resonance spectroscopy (sMRI);

and positron emission tomography (PET). Each of these technologies yields different information and some may even be combined.

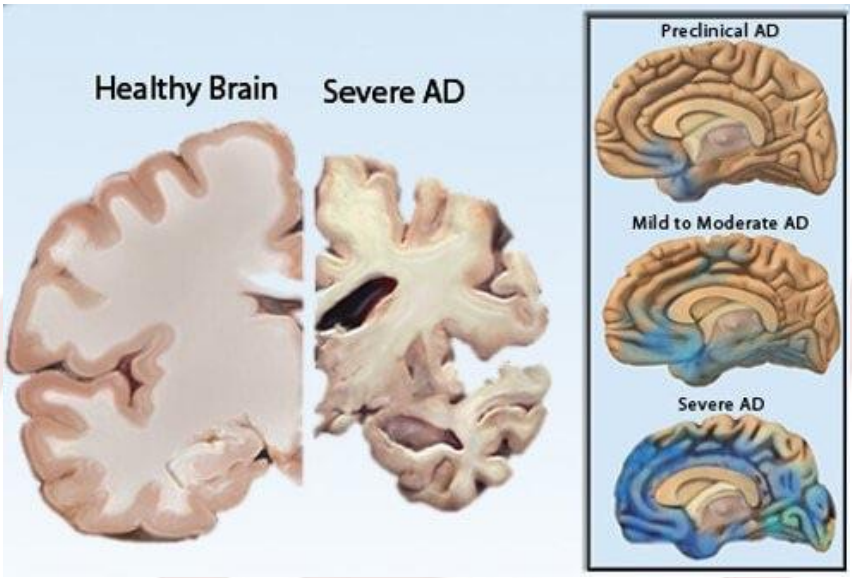
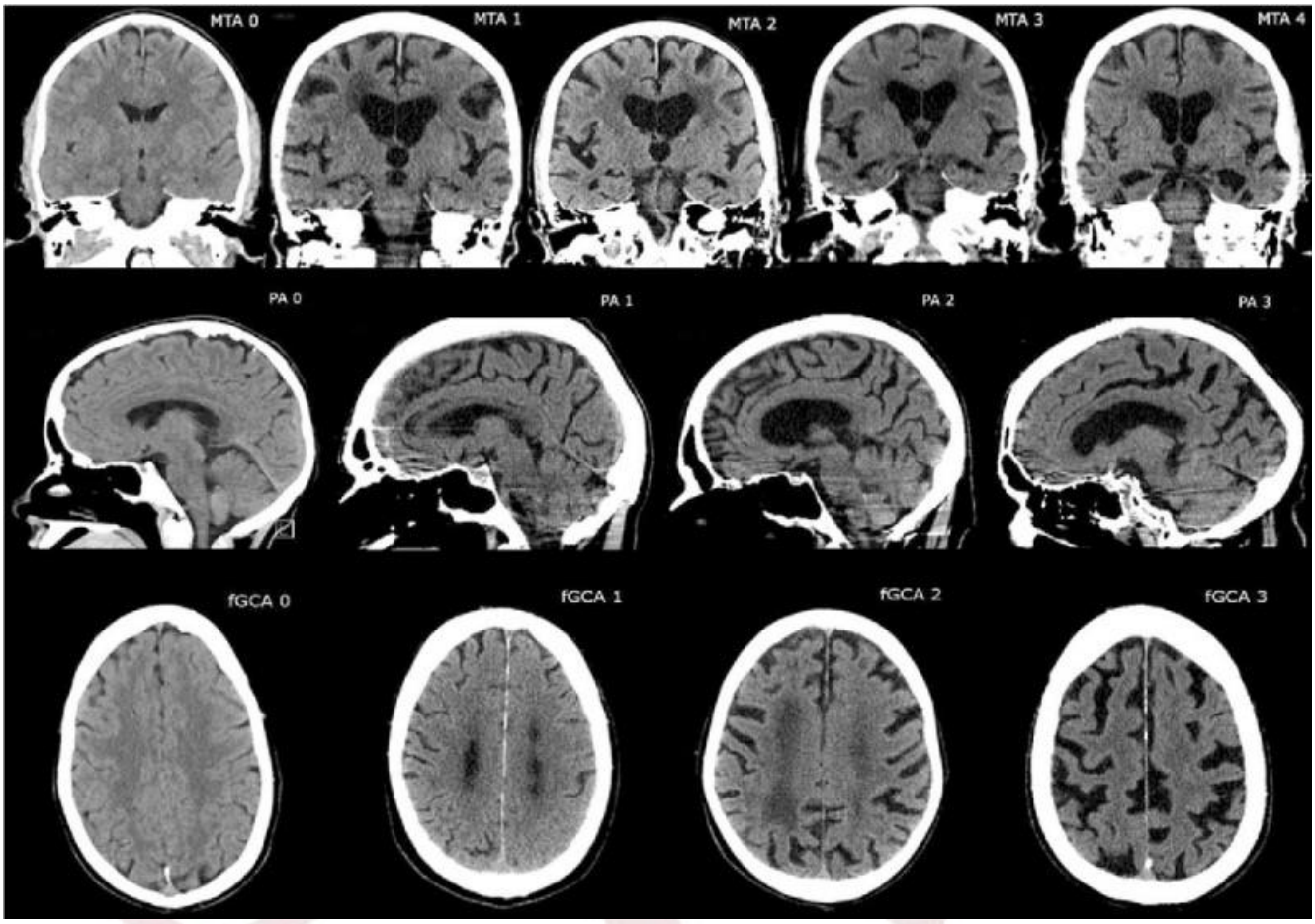


Figure 4: Brain shrinkage from preclinical AD to mild-to-moderate AD to severe AD

For example, MRI is a radiological imaging technique used to form pictures of the anatomy and the physiological processes of the body in both health and disease. The scanners employed to produce such images use strong magnetic fields, magnetic field gradients, and radio waves to generate the images.

The technique does not involve X-rays or ionizing radiation, distinguishing it from CT or CAT. On the other hand, PET is a nuclear medicine functional imaging technique that is used to observe metabolic processes in the brain (and more generally in the body) to aid in the diagnosis of disease. The system detects pairs of gamma-rays emitted indirectly by a positron-emitting radioligand, most commonly fluorine-18, which is introduced into the body on a biologically active molecule called a radioactive tracer.

Metabolic trapping of the radioactive glucose molecule allows the PET scan to be utilized and different ligands may be used for different imaging purposes. Three-dimensional images of tracer concentration within the body region of interest are then constructed by computer analysis.



(MTLA=Medial temporal lobe atrophy; PA=Posterior atrophy; fGCA=Frontal cortical atrophy)

Figure 5: Head CT images of various grades of cerebral atrophy

Figure 5 is an example of CT images showing cerebral atrophy with different grading systems (observe the decreased size of the gyri and the secondary increased size of the sulci). While the hazards of X-rays are nowadays generally well-controlled in most medical contexts, an MRI scan may still be seen as a better choice than a CT scan. It is widely used in hospitals and clinics for medical diagnosis, staging of disease, and follow-up without exposing the body to radiation. On the other hand, an MRI may yield different information compared with CT and there may be risks and discomforts associated with it. Further, compared with CT, MRI typically takes longer, is louder, and needs the subject to enter a narrow, confining tube. In addition, people with medical or/and dental implants or other non-removable metal inside their body may be unable to undergo an MRI examination safely.

Considering the crucial importance of PET in the imaging of AD, I will provide several illustrations of it. Figure 6 is a sample PET brain image of a 56-year old patient (male). If the chosen biologically active tracer molecule is fludeoxyglucose, an analogue of glucose, the concentrations of tracer imaged will indicate tissue metabolic activity as they correspond to the

regional glucose uptake. In the Figure, the red areas show more accumulated tracer substance whereas the blue areas are regions where low to no tracer have been accumulated. Use of this tracer to explore the possibility of cancer metastasis (i.e., spreading to other sites) is the most common type of PET scan in standard medical care (representing ~ 90% of current scans). The same tracer may also be used for PET investigation and diagnosis of types of dementia. Less often, other radioactive tracers, usually but not always labeled with fluorine-18, are used to image the tissue concentration of other types of molecules of interest.

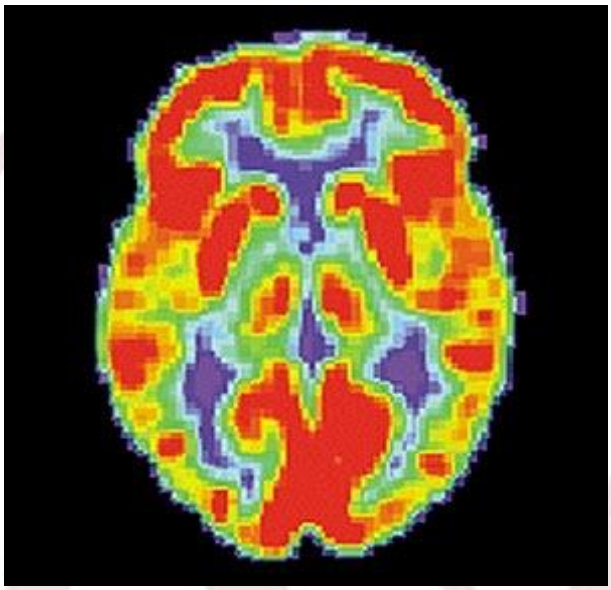


Figure 6: A sample brain PET image

Figure 7 illustrates AD effects in several brain areas (observe the several colored areas) and Figure 8 is the PET image of a diseased person's brain. One of the disadvantages of PET scanners is their operating cost. SPECT, which is a similar imaging process to PET, also uses radioligands to detect molecules in the brain. I will not discuss or illustrate here SPECT or its use for imaging neurodegenerative diseases, including AD. Likewise, however useful they are, I will not consider fMRI, MRA and MRS that complement MRI and may respectively be employed to investigate brain physiology, blood circulation within the brain, and its metabolites.

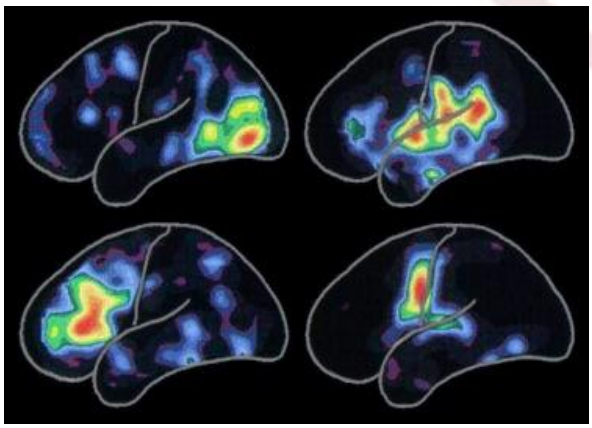


Figure 7: PET images illustrating AD effects in several brain areas

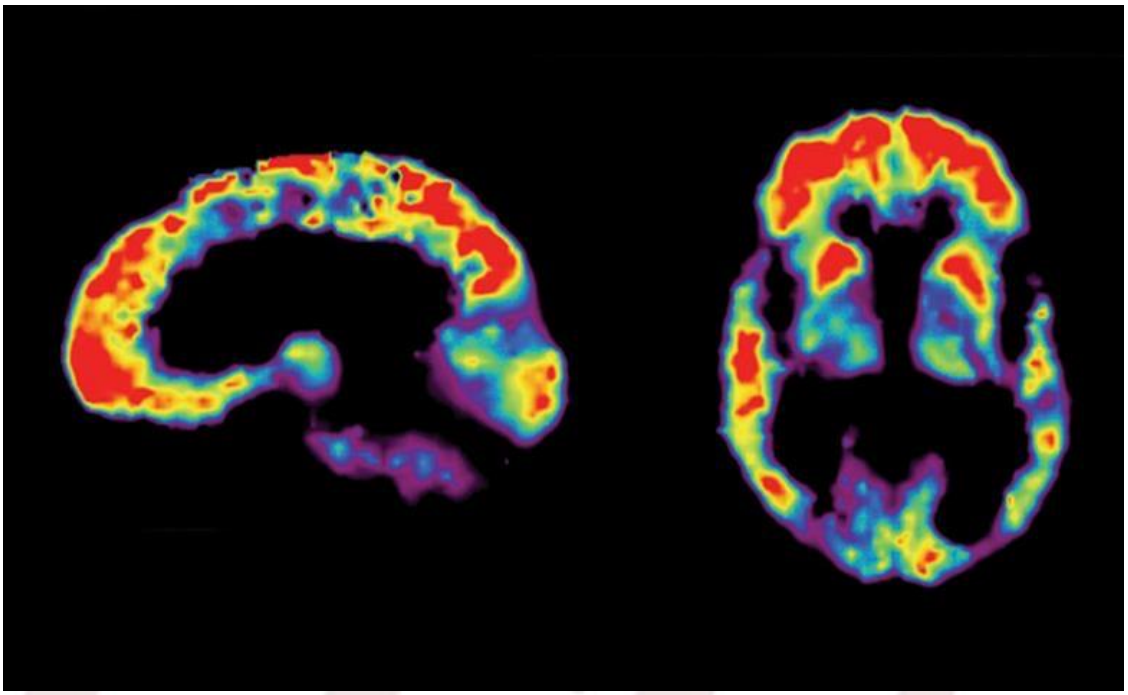


Figure 8: PET image of a diseased person's brain

Figure 9 further contrasts PET images of a normal brain (left) to a brain with mild cognitive impairment (center) and an Alzheimer-diseased brain (right) and an Alzheimer-diseased brain (right).

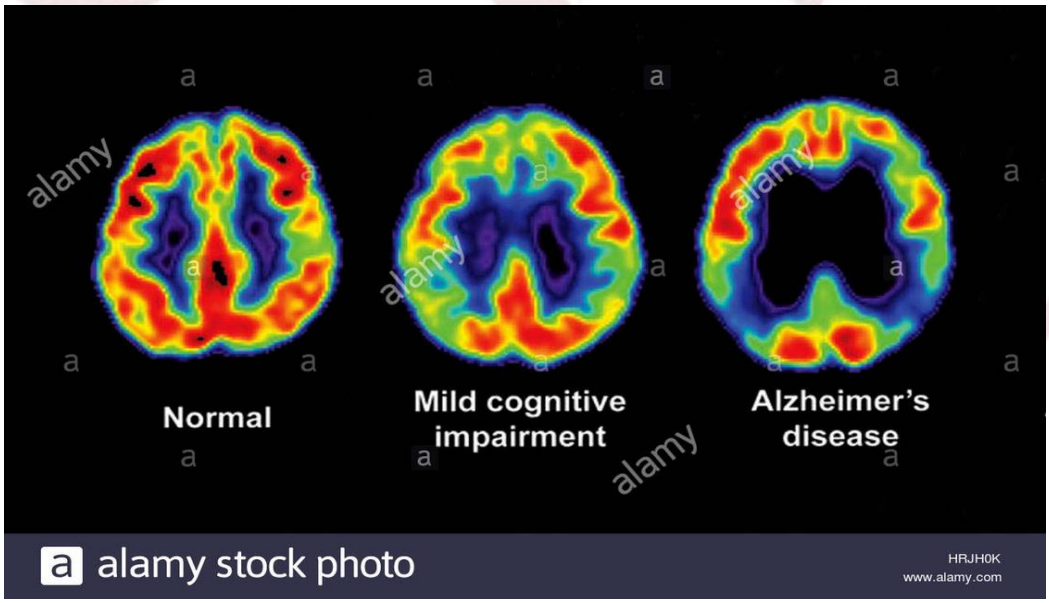
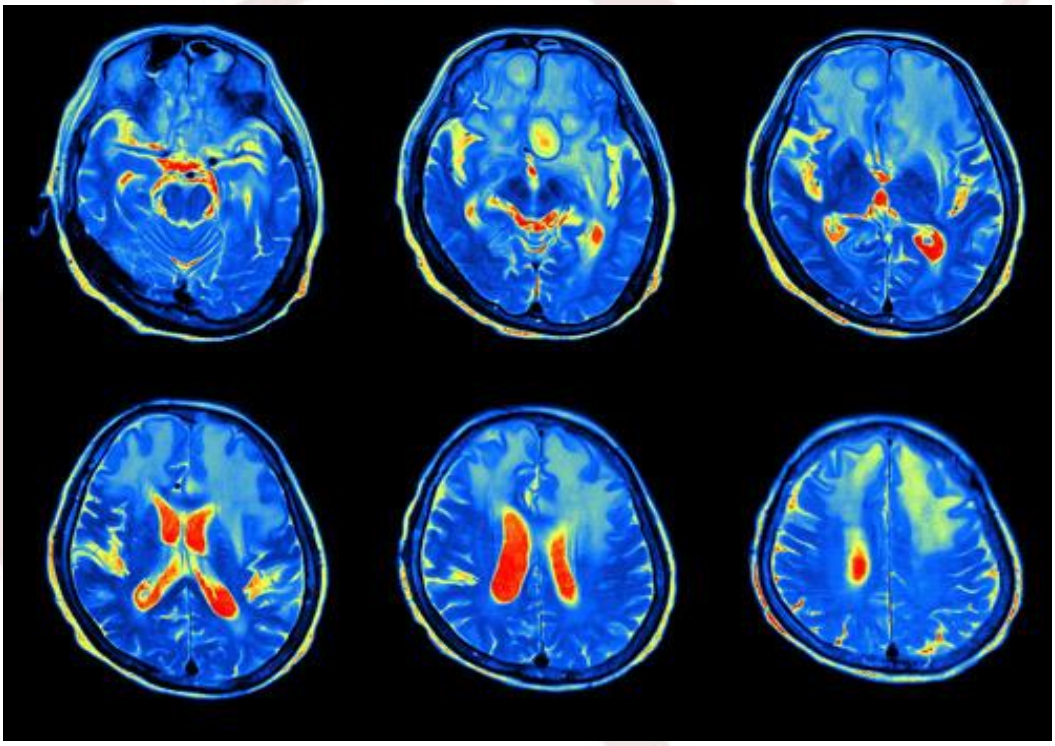


Figure 9: PET images contrasting a normal brain (left) to a brain with mild cognitive impairment (center) and an Alzheimer-diseased brain (right)

In this context, a few words of praise should be formulated regarding the United Kingdom Biobank. The biobank holds genetic, physical, and clinical data from a large cohort of individuals (by 2010, ~ 500,000 individuals age 40-69 at recruitment, and scheduled to increase to 5 million). Following this age group has enabled to focus on diseases of middle age and later including genetic influences on NDDs such as AD. In 2018, it reported a study of brain images of 10,000 individuals, which revealed genetic influences on brain structure and function, and showed correlations with neurodegenerative, psychiatric, and personality traits. This trove of data is available free of charge to scientific researchers for the pursuit of a variety of research projects aimed at better understanding AD and other NDDs, and hopefully developing diagnostic and therapeutic procedures for such diseases. From such data, the cohort of axial brain MRI images of Figure 10 images was obtained.



Source: UK Biobank

Figure 10: A cohort of axial brain MRI images

At the Jülich Institute of Neurosciences and Biophysics in Germany, the world's largest and most powerful PET-MRI device began operation in April 2009. Presently, only the head and brain can be imaged at the high magnetic field strengths employed. For brain imaging, because of the absence of motions, registration of CT, MRI and PET scans may be accomplished without the need for an integrated PET-CT or PET-MRI scanner by using a device known as the N-localizer. Figure 11 shows fused PET/CT and PET/MRI technologies for brain imaging.

With all these advanced technologies, whether singly or in combination, it is possible to accurately diagnose AD and monitor its ineluctable progression. When treatments and (hopefully) even a cure will be available, the same technologies will also enable us to follow their efficacy and personalize them to the patients.

Figure 11: Fused PET/CT and PET/MRI technologies for brain imaging

What is brain fog and what can be done about it?

Brain fog is a lay term to describe fluctuating mild memory loss that is inappropriate for a person's age. It may include forgetfulness, spaciness, confusion, decreased ability to pay attention, inability to focus, and difficulty in processing information. This is more than the gradual cognitive decline taking place from early adulthood that is a fact of life.

Brain fog can also occur in Sjögren's syndrome (SS). Recent scientific data show that longevity is associated with the successful management of chronic diseases, such as SS, not the absence of any disease! A major cause of cognitive dysfunction can be side effects of drugs and drug interactions, especially in patients over 65-70 years of age; but other factors that might be causing these symptoms should also be considered.

Managing one's lifestyle to optimize one's health and sense of well-being and developing a close working relationship with one's doctor(s) are recommended actions against brain fog. These include: Always reporting changes in cognition/memory and mood

(depression, anxiety) and training and boosting one's brain power. Considerably more details can be found in my book on this subject (see the References section).

Conclusions and take-aways

- Forgetfulness is common and happens to most people, including memory champions. Distraction, fatigue, depression, anxiety, absent-mindedness, and many other factors may contribute to it.

- Most episodes of forgetfulness are simply temporary and not a harbinger of Alzheimer's, dementia or other memory disorder. Such episodes are frequently linked to situational factors and normal age-related changes.

- Because memory impacts nearly every aspect of daily life, and because the incidence of Alzheimer's and other memory disorders also increases with age, it becomes important to distinguish between normal age-related memory changes and signs of a memory disorder.

- The vast potential of the human brain becomes especially clear in the domain of memory. The most captivating instances of superior memory ability may be few and far between. Hyperthymesia is a condition that leads people to be able to remember an abnormally large number of their life experiences in vivid detail. Highly superior autobiographical memory is the ability to remember far more about one's own life than is typical, including details of personal experiences and when they occurred.

- Whether or not forgetfulness is a "brain blip" or a sign of a potential memory problem, it is never too late to start building better brain health.

- With increasing lifespan in the developed world, dementia has become an increasing public health concern. But dementia is not an emerging disease! To this day, the causal etiology of many types of dementia still remains unclear and their cure elusive.

- Dementia is a general term for the process of decline in mental abilities. It is a broad category of brain diseases that cause a long-term and often gradual decrease in the ability to think and remember that is great enough to affect a person's daily functioning. Although age is the strongest known risk factor, dementia is not an inevitable consequence of aging. Risk factors include existing medical conditions and lifestyle choices.

- Many different diseases can cause dementia, including Alzheimer's disease, vascular disease, Lewy bodies, frontotemporal disorders, syphilis, senility, and even stroke. Mixed dementia is the concurrence of two or more types of dementia.

- While we continue to unravel the complex brain changes involved in the onset and progression of Alzheimer's, it seems likely that damage to the brain started a decade or more before memory and other cognitive problems appeared. Many molecular and cellular changes take place in the brain, particularly in the hippocampus. As more neurons die, additional parts of the brain are affected, and they begin to shrink. By the final stage, damage and the brain structure and convolutions are distorted with extreme shrinkage.

- Brain fog describes the fluctuating mild memory loss that is inappropriate for a person's age. It is more than the gradual cognitive

decline taking place from early adulthood. Managing one's lifestyle to optimize one's health and sense of well-being are recommended actions.

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