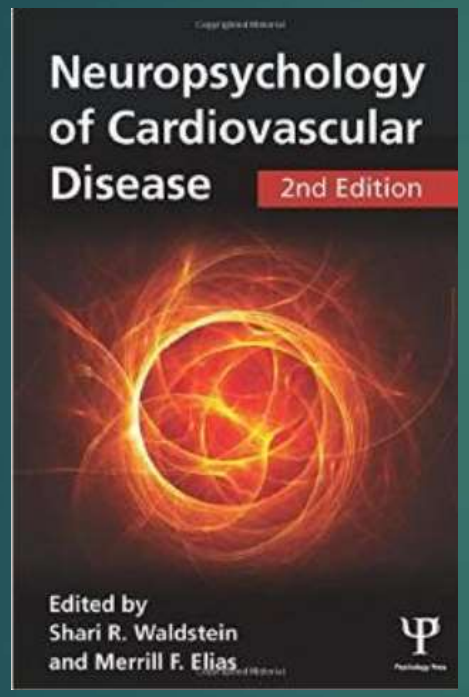
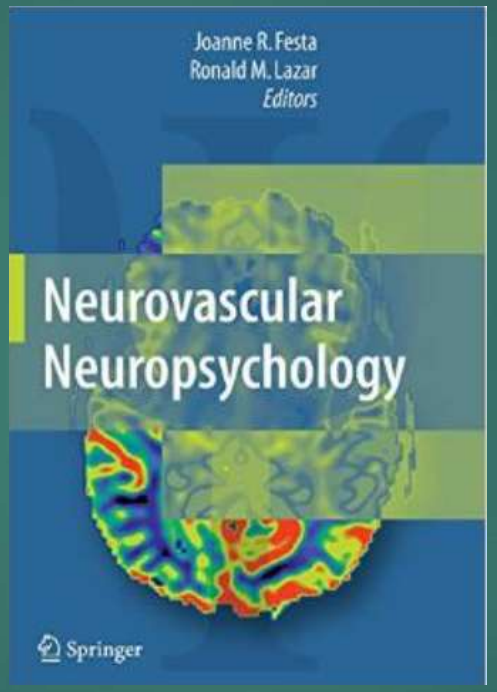
Neurovascular Neuropsychology

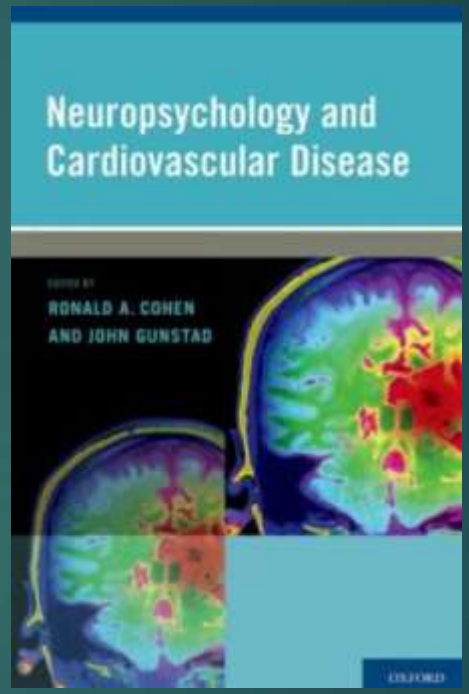
CHARLES J. VELLA, PH.D.

JANUARY, 2018

The Texts





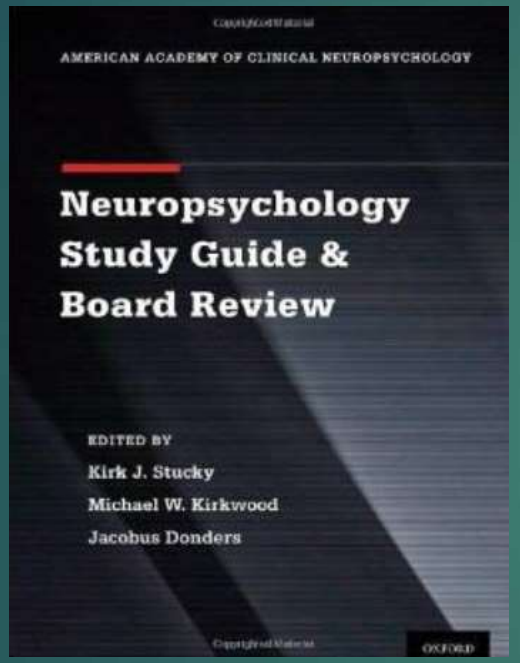


S.Waldstein & M. Elias (Editors) 2015

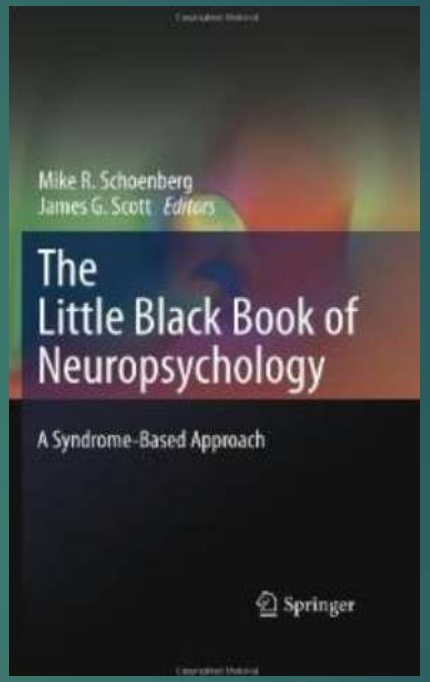
J. Festa & R. Lazar, (Editors) 2009

- Ronald Cohen &
- John Gunstad 2010

Two Major References



K J. Stucky, M Kirkwood & Donders, 2013



M Schoenberg & J G Scott, 2011

What is bad for the heart is bad for the brain.

Remember: Heart ↔ Brain

- Anything that is good for heart is good for the brain
- Anything that negatively effects the heart negatively effects the brain
- Cardiovascular health is good for the brain
- Physical exercise is the most powerful brain fitness recommendation for all neurological disorders

Brain Vasculature

400 miles of blood vessels

Brain and Cardiovascular System

- Brain is particularly dependent on supply of blood: Despite being only 2% of body, brain uses 20% of cardiac output each minute
- The brain needs a continuous blood supply, and interruption of cerebral blood flow (CBF) leads to brain dysfunction and death
- Decreased CBF precede signs and symptoms of CVD by 2 years
- 1 in 4 (60 million) have CVD

CV Basics – CV autoregulation

- Cerebrovascular autoregulation keeps CBF relatively constant within a range of blood pressures, protecting the brain from unwanted swings in perfusion pressure.

- In animal models, the major risk factors for VCI and Alzheimer disease—hypertension, aging, and diabetes—impair endothelium-dependent responses in the cerebral microcirculation and blunt functional hyperemia (increase in blood flow).

- Beta Amyloid is a potent vasoconstrictor and suppresses endothelium-dependent responses and cerebrovascular autoregulation.

Arteries

- Topography of major arteries and their connection determine the location of brain dysfunction caused by a cerebrovascular event.

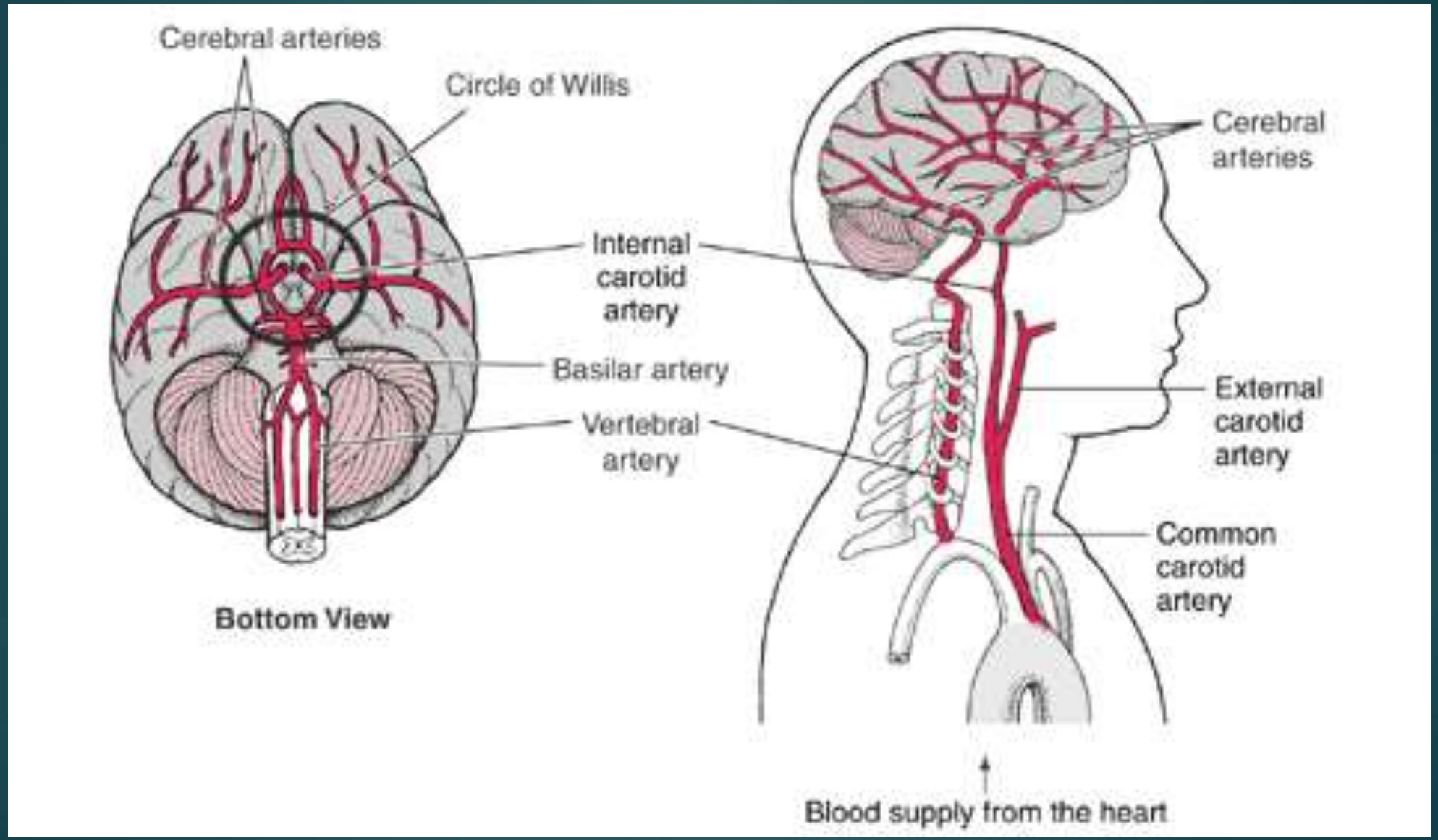
Brain Circulation

- Carotid & vertebral arteries bring blood to brain from heart.
- Each carotid artery divides into external and internal segments at the thyroid cartilage.
- At level of optic nerve, internal carotid divides into anterior and middle cerebral arteries.

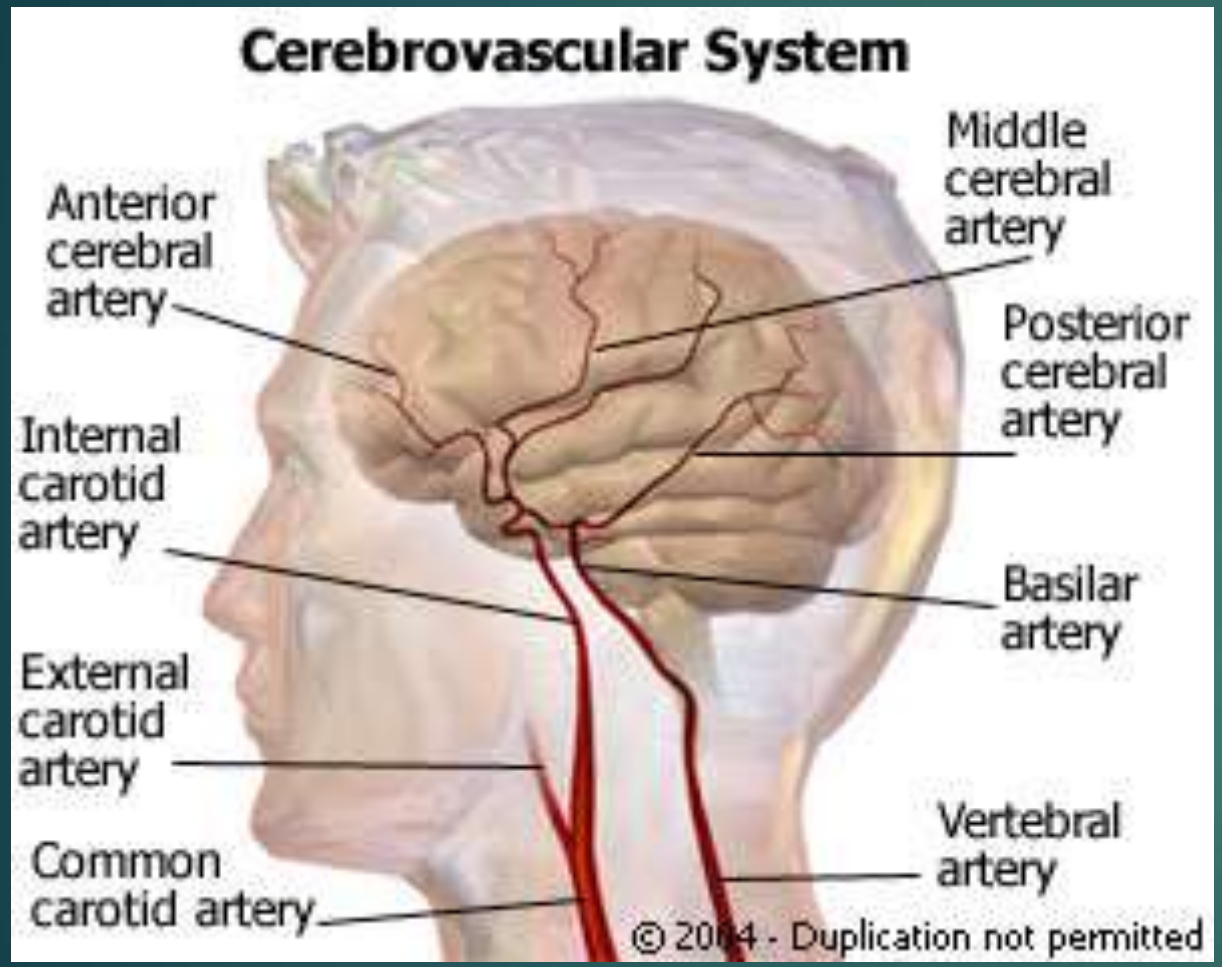
Brain Circulation 2

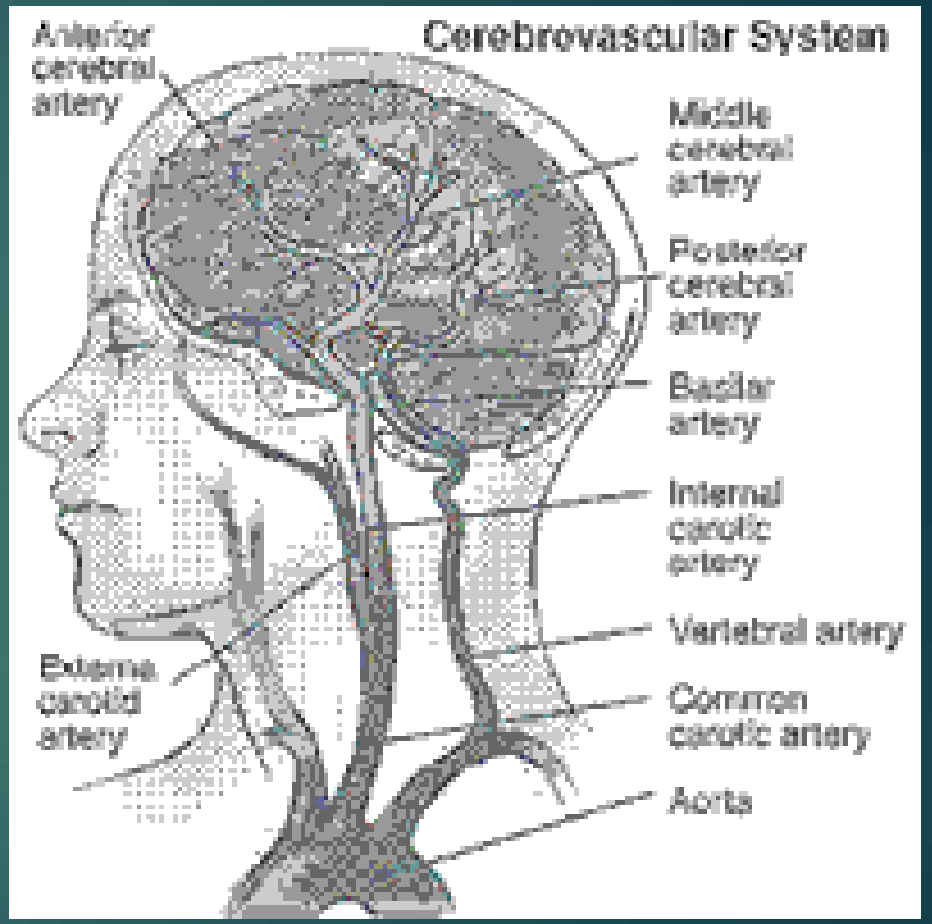
- The vertebral arteries ascend thru the spinal vertebrae and join in the lower pons to form the basilar artery
- At the Circle of Willis, the basilar artery divides to form the posterior cerebral arteries (blood to inferior temporal gyrus, part of occipital lobe, and parts of superior parietal lobe.)
- Vertebrobasilar system and posterior cerebral artery supply brain stem, cerebellum, thalamus, occipital lobes, and posterior temporal lobes.

The cerebrovascular system

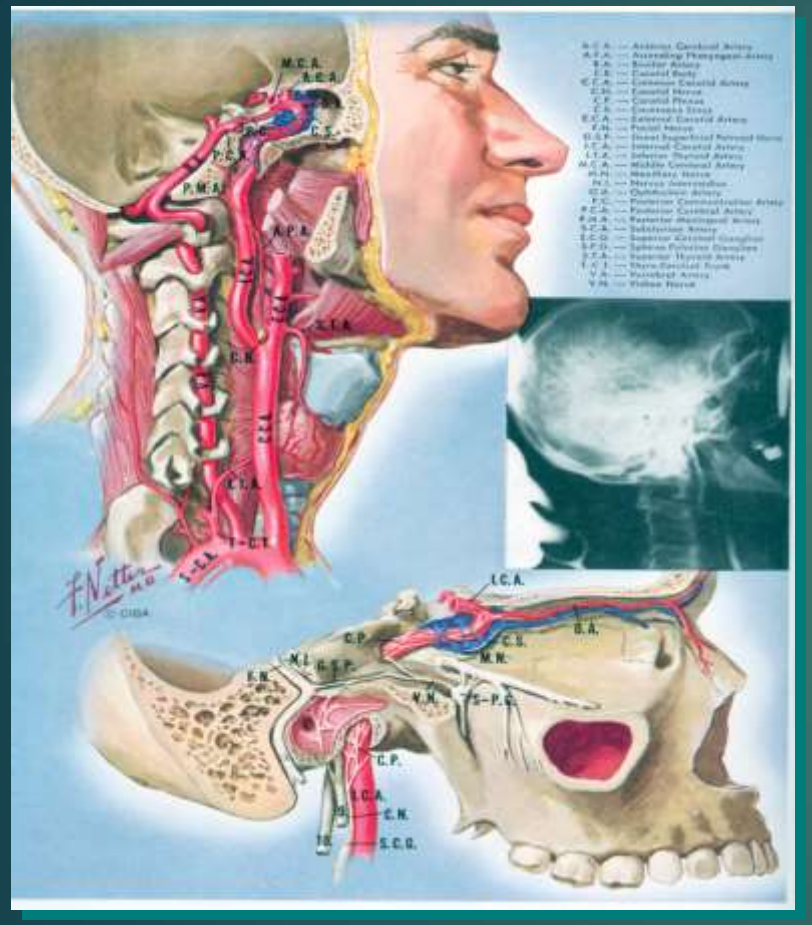


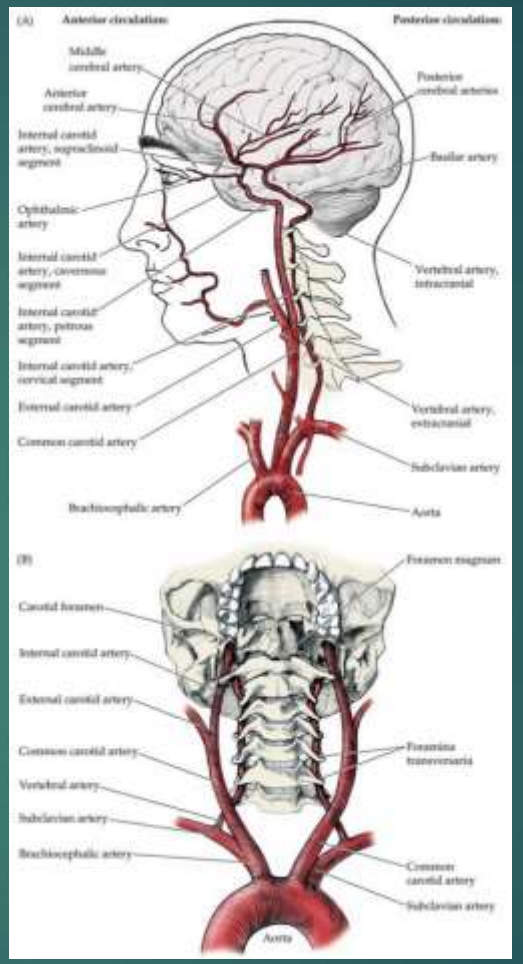
Cerebrovascular System





Blood Supply: Internal Carotid, Basilar, Carotid, Vertebral Arteries



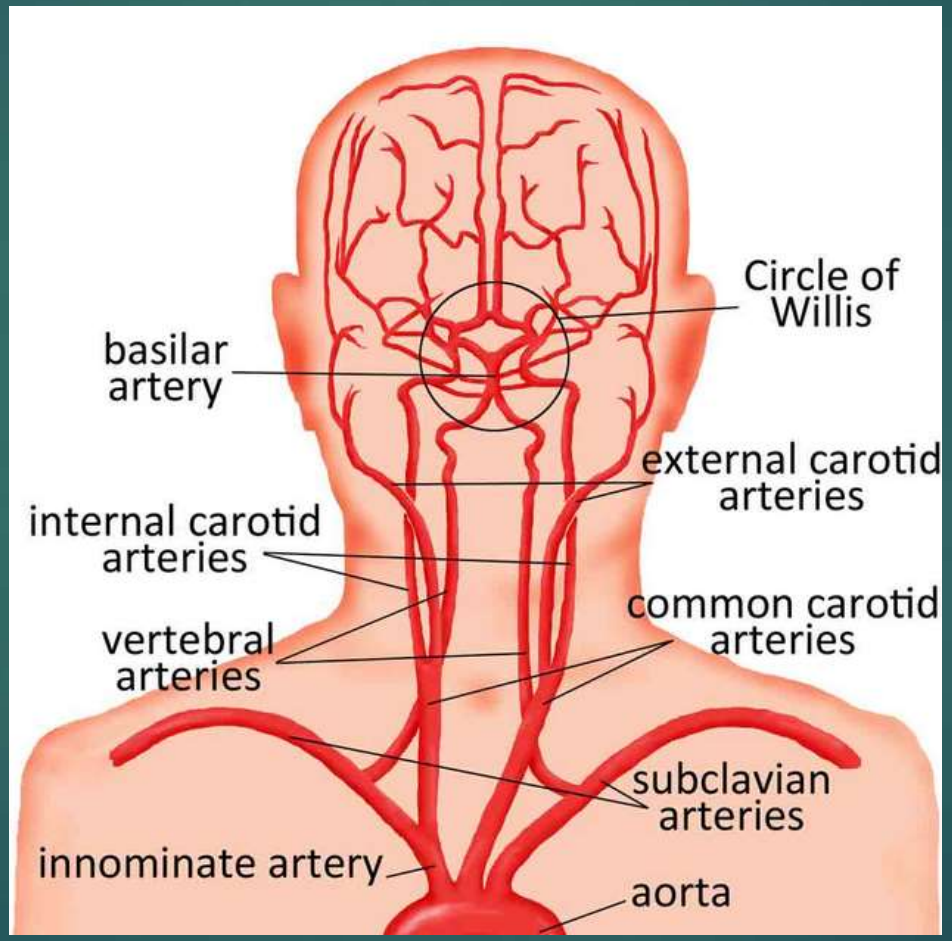


<u>Never let chiropractor do a neck adjustment</u>: basilar stroke

Blood Supply to Brain

Anterior supply:
Internal carotids

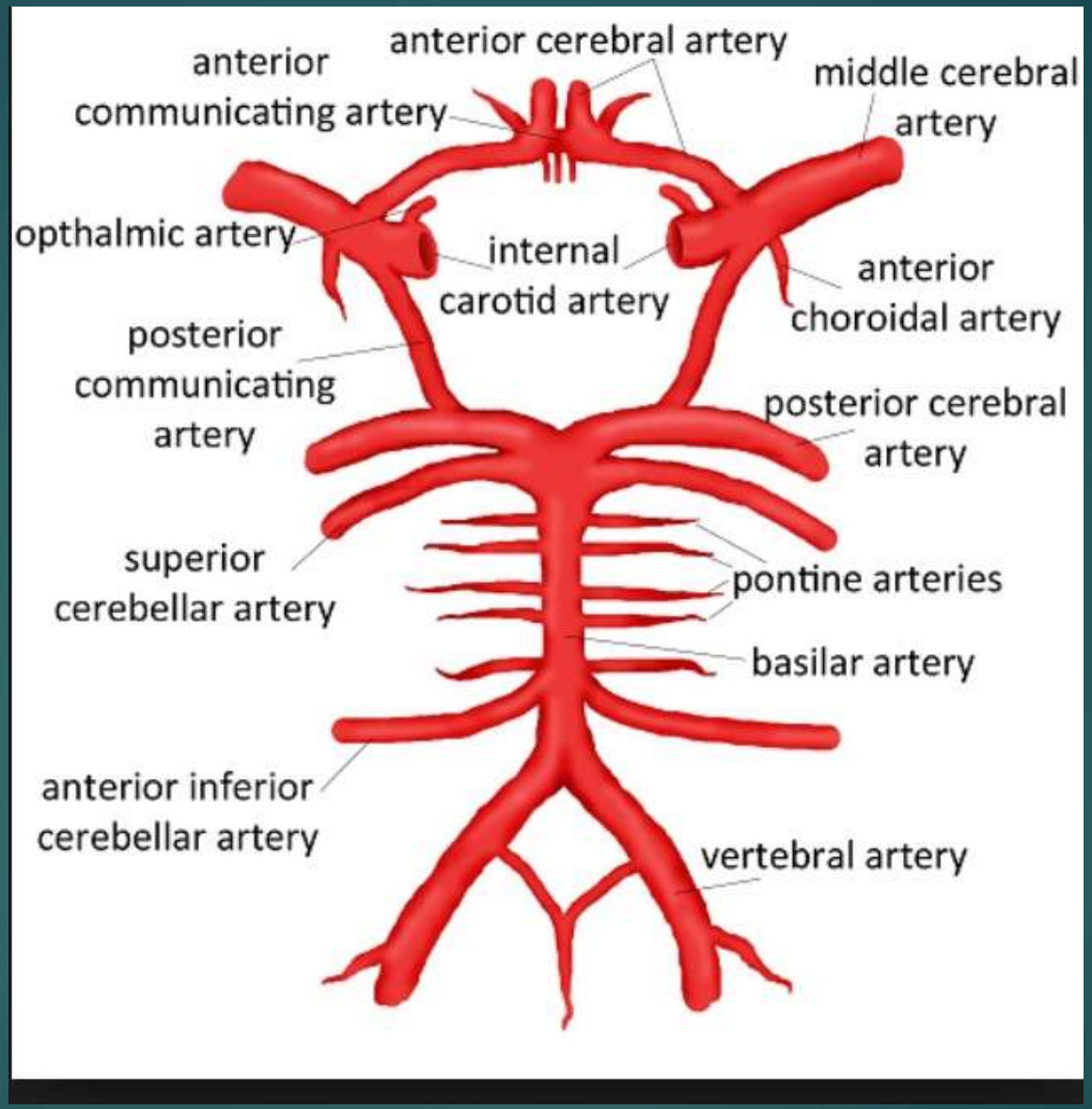
To ACA & MCA



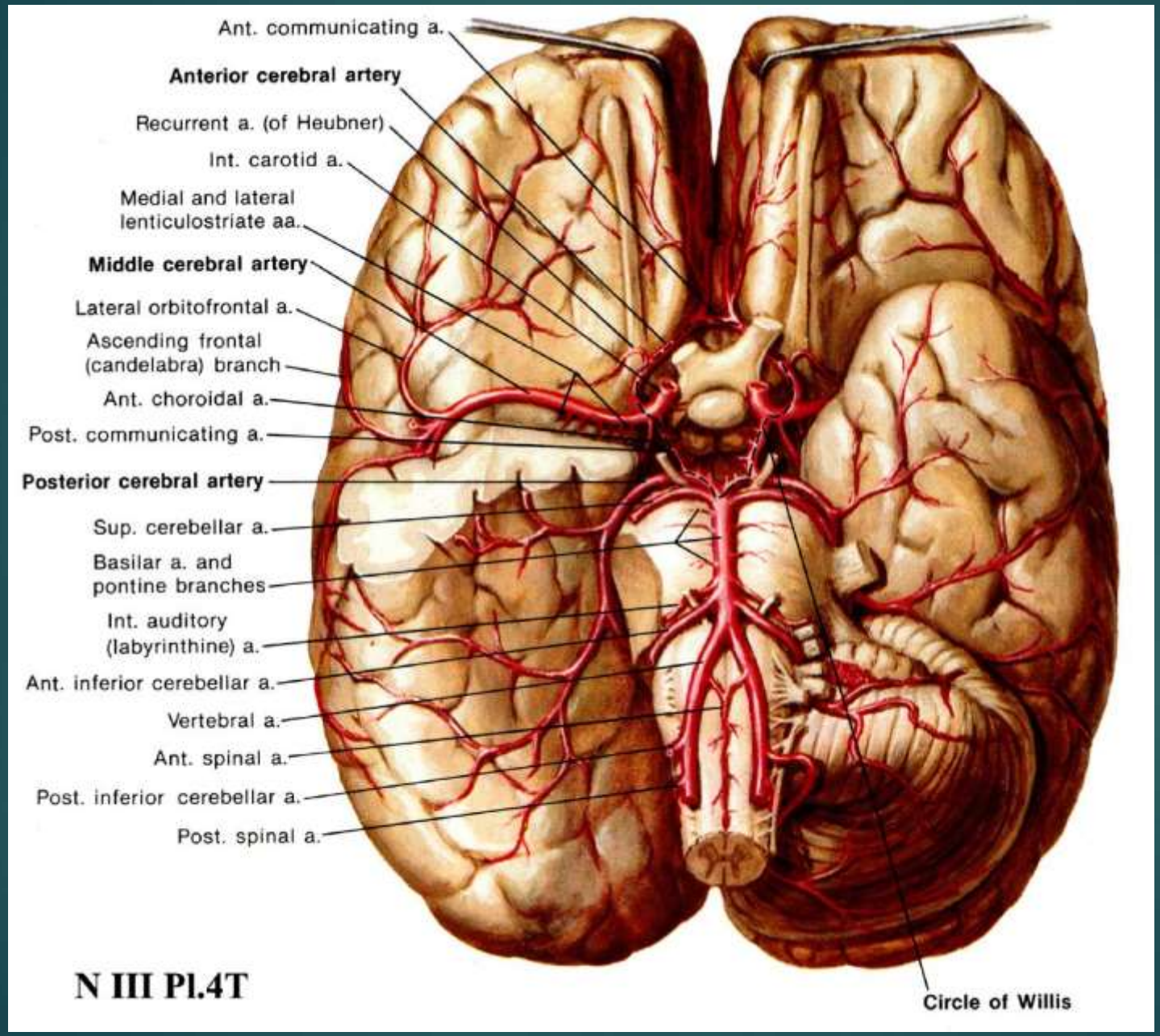
Posterior supply:
Vertebral &
Basilar

To PCA

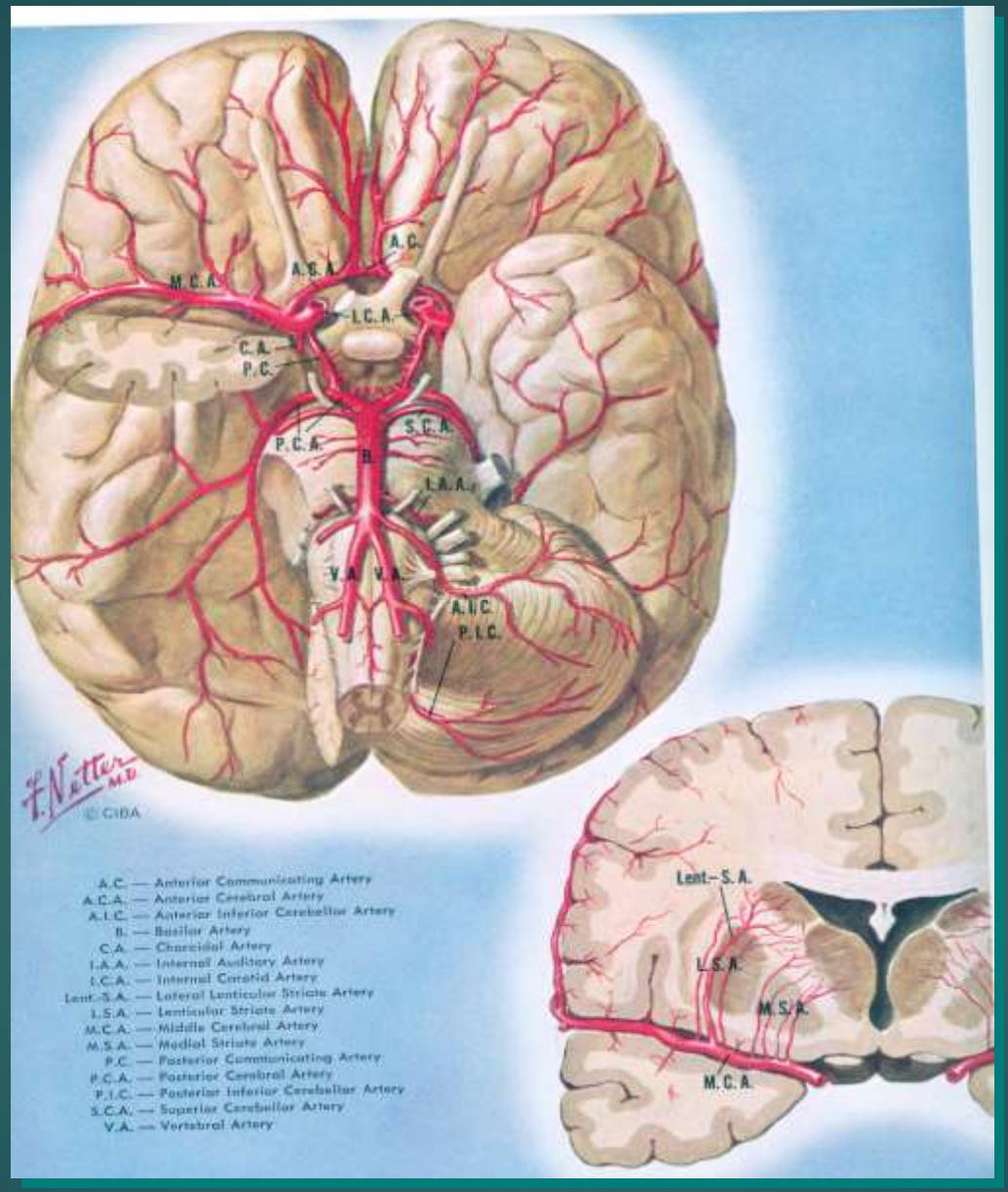
Circle of Willis



40% have incomplete Circle of Willis


Ant. communicating a.
Anterior cerebral artery
Recurrent a. (of Heubner)
Int. carotid a.
Medial and lateral lenticulostriate aa.
Middle cerebral artery
Lateral orbitofrontal a.
Ascending frontal (candelabra) branch
Ant. choroidal a.
Post. communicating a.
Posterior cerebral artery
Sup. cerebellar a.
Basilar a. and pontine branches
Int. auditory (labyrinthine) a.
Ant. inferior cerebellar a.
Vertebral a.
Ant. spinal a.
Post. inferior cerebellar a.
Post. spinal a.
N III Pl.4T
Circle of Willis

Circle of Willis



Venous System: removal of deoxygenated blood

Flow into series of sinuses in spaces left between meninges (dura)

Sinus = vein

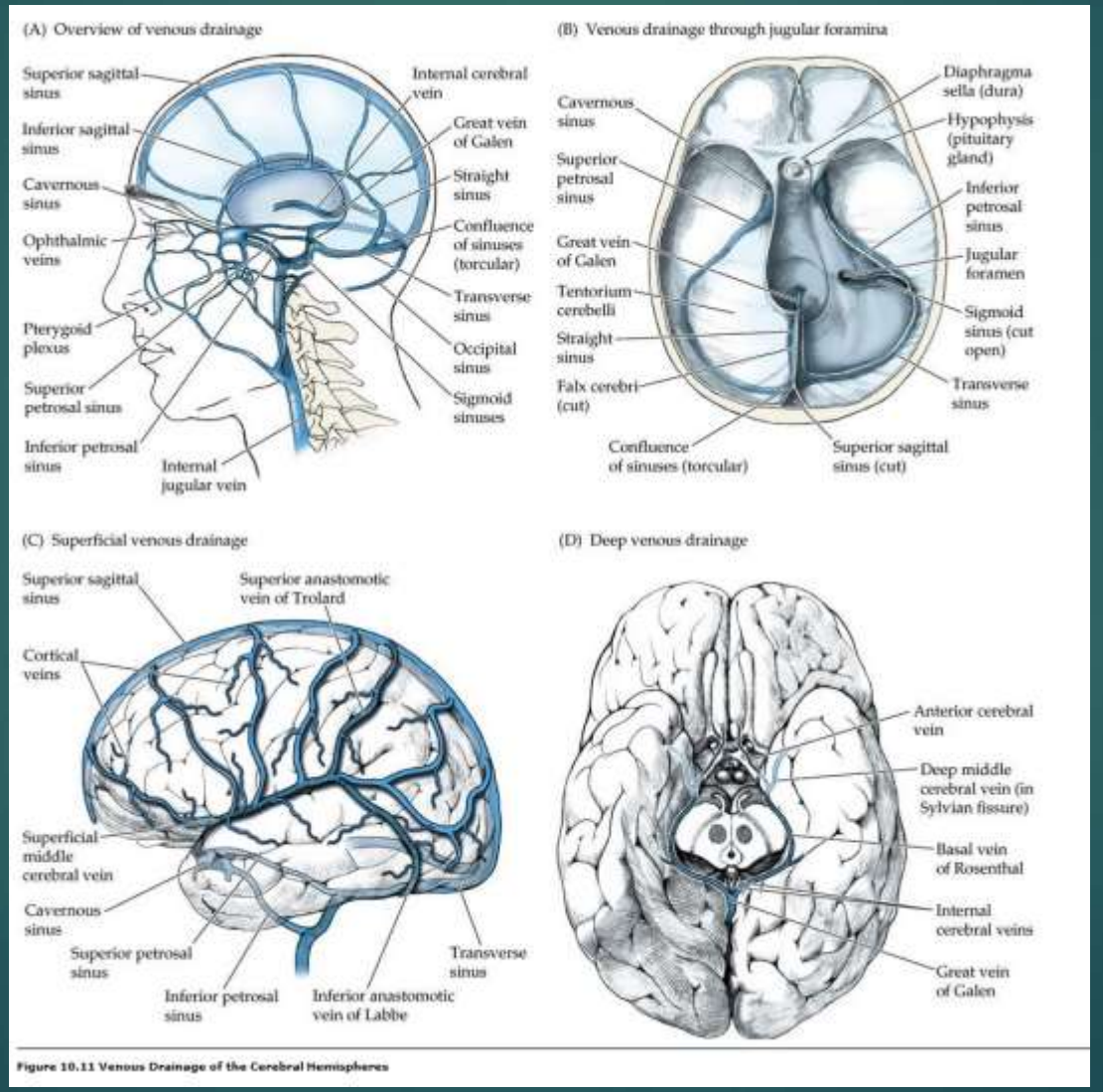
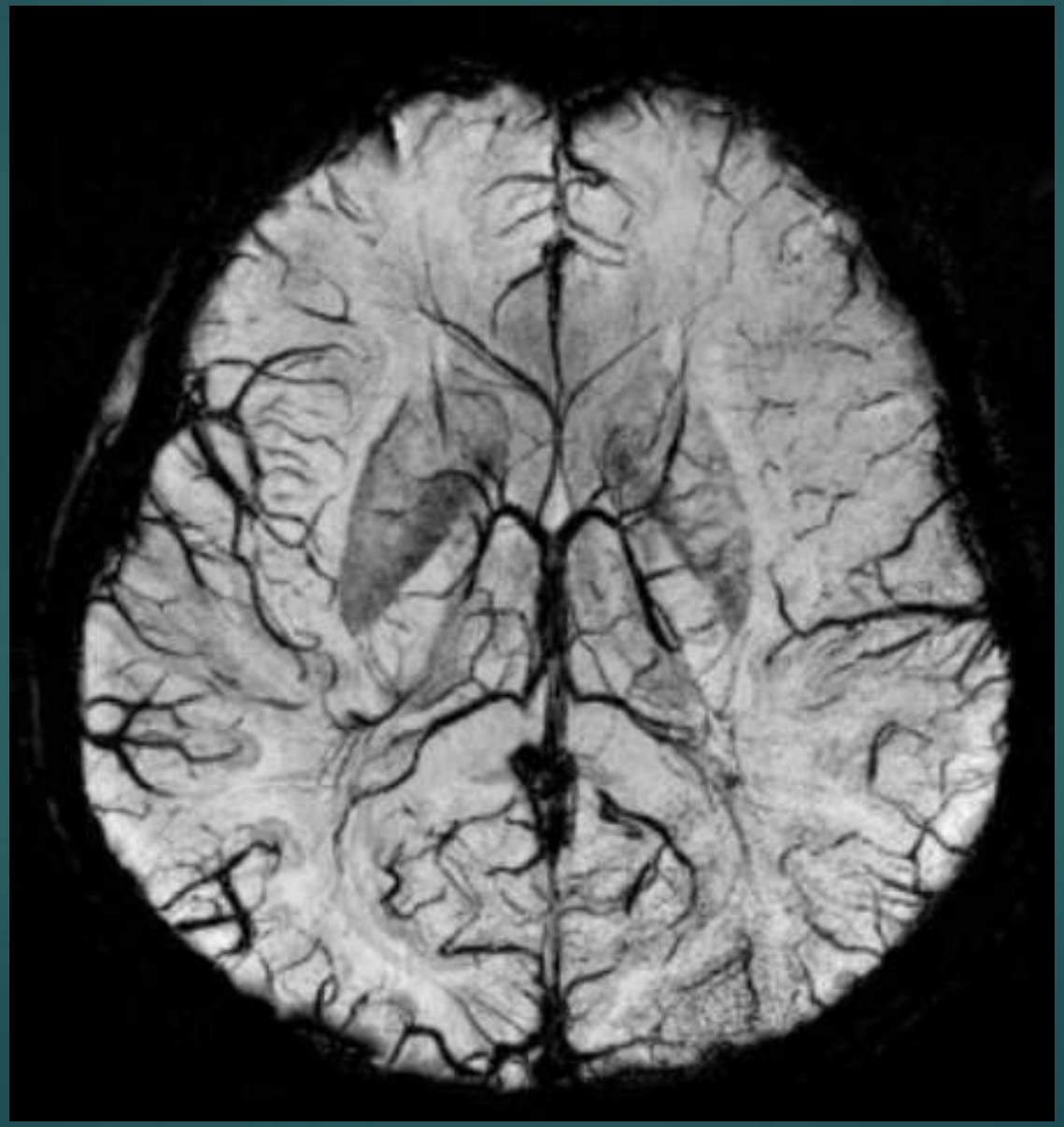


Figure 10.11 Venous Drainage of the Cerebral Hemispheres

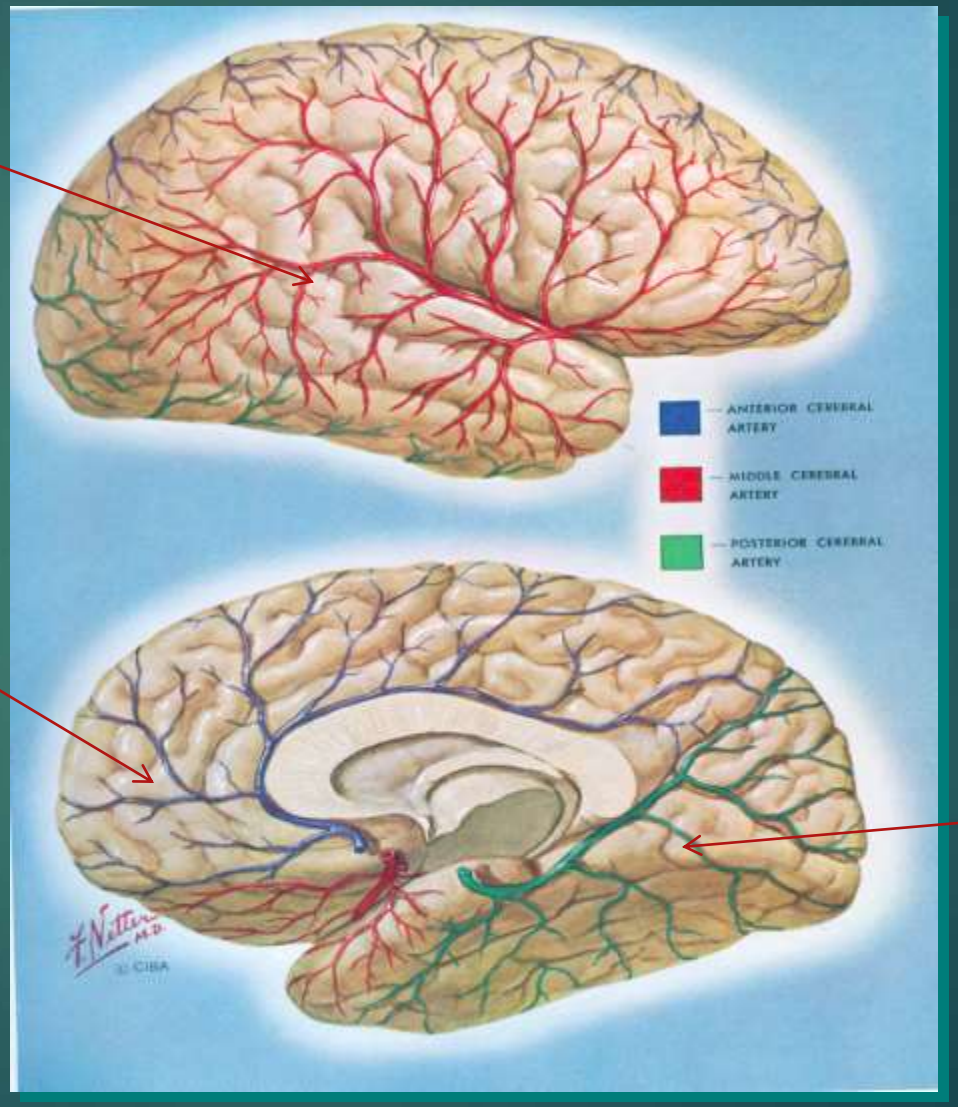
Susceptibility weighted imaging (SWI) of veins in brain



Blood Supply 2: ACA, MCA, PCA

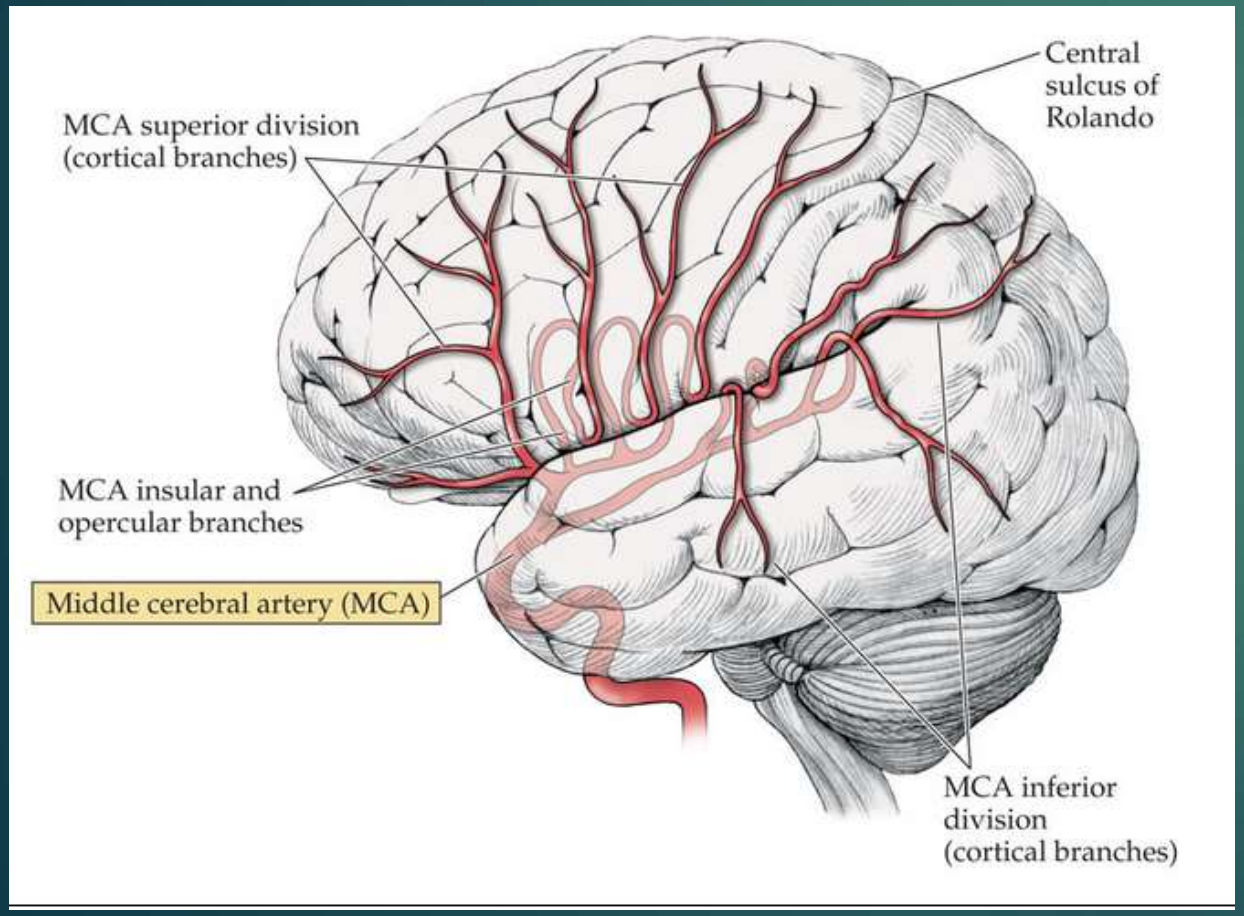
MCA

ACA



PCA

MCA, ACA, PCA



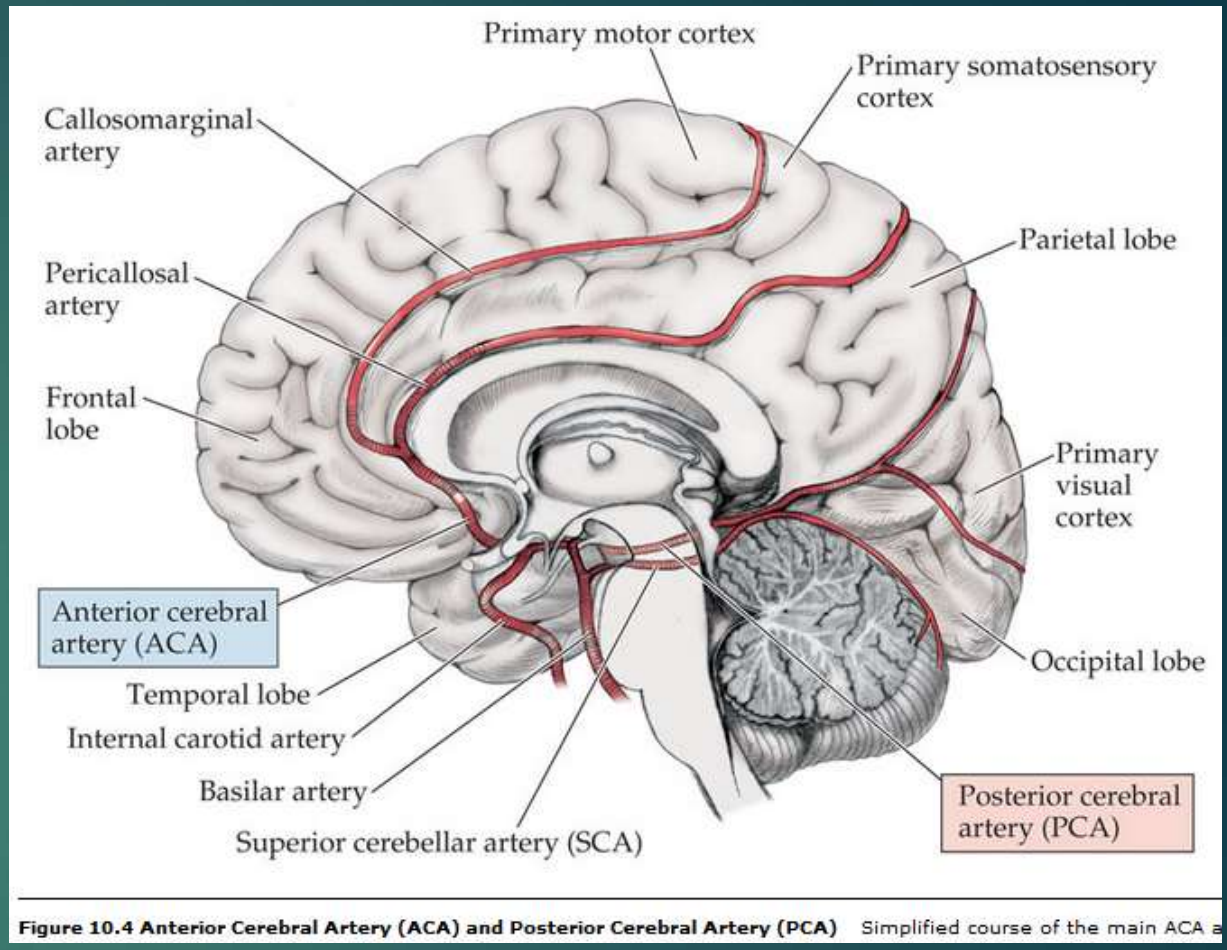
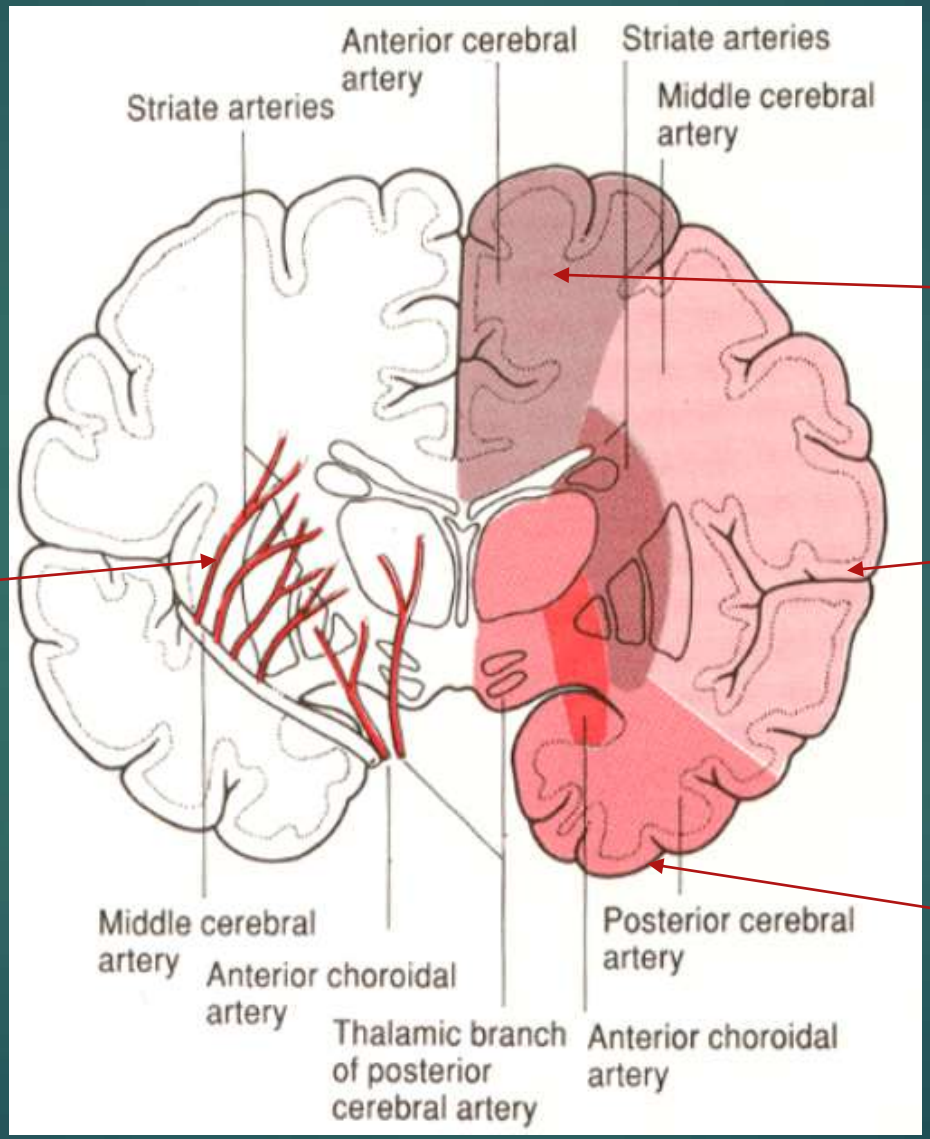


Figure 10.4 Anterior Cerebral Artery (ACA) and Posterior Cerebral Artery (PCA) Simplified course of the main ACA a

Basal Ganglia Blood Supply: Striate arteries

Basal Ganglia Blood Supply

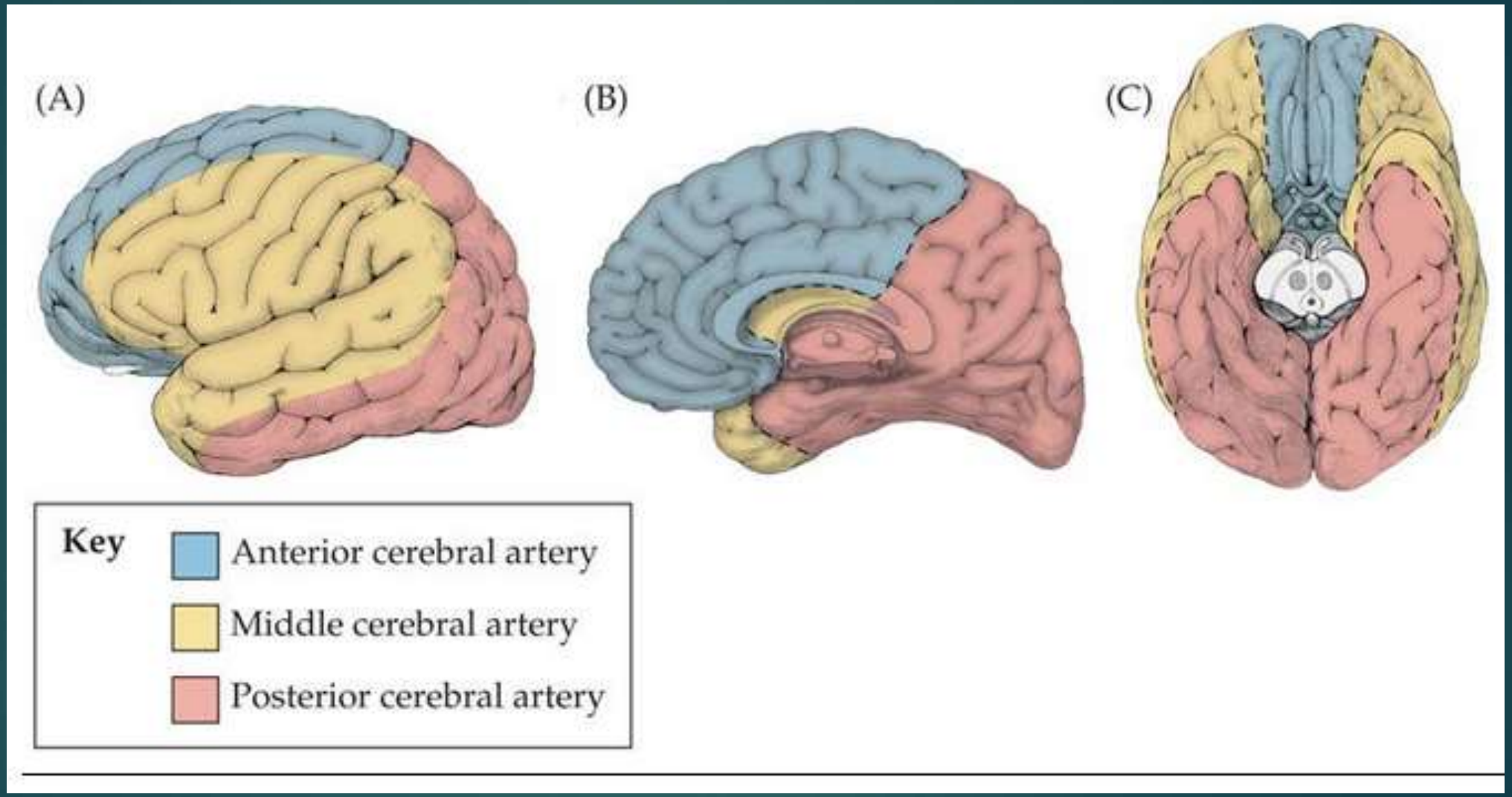


ACA

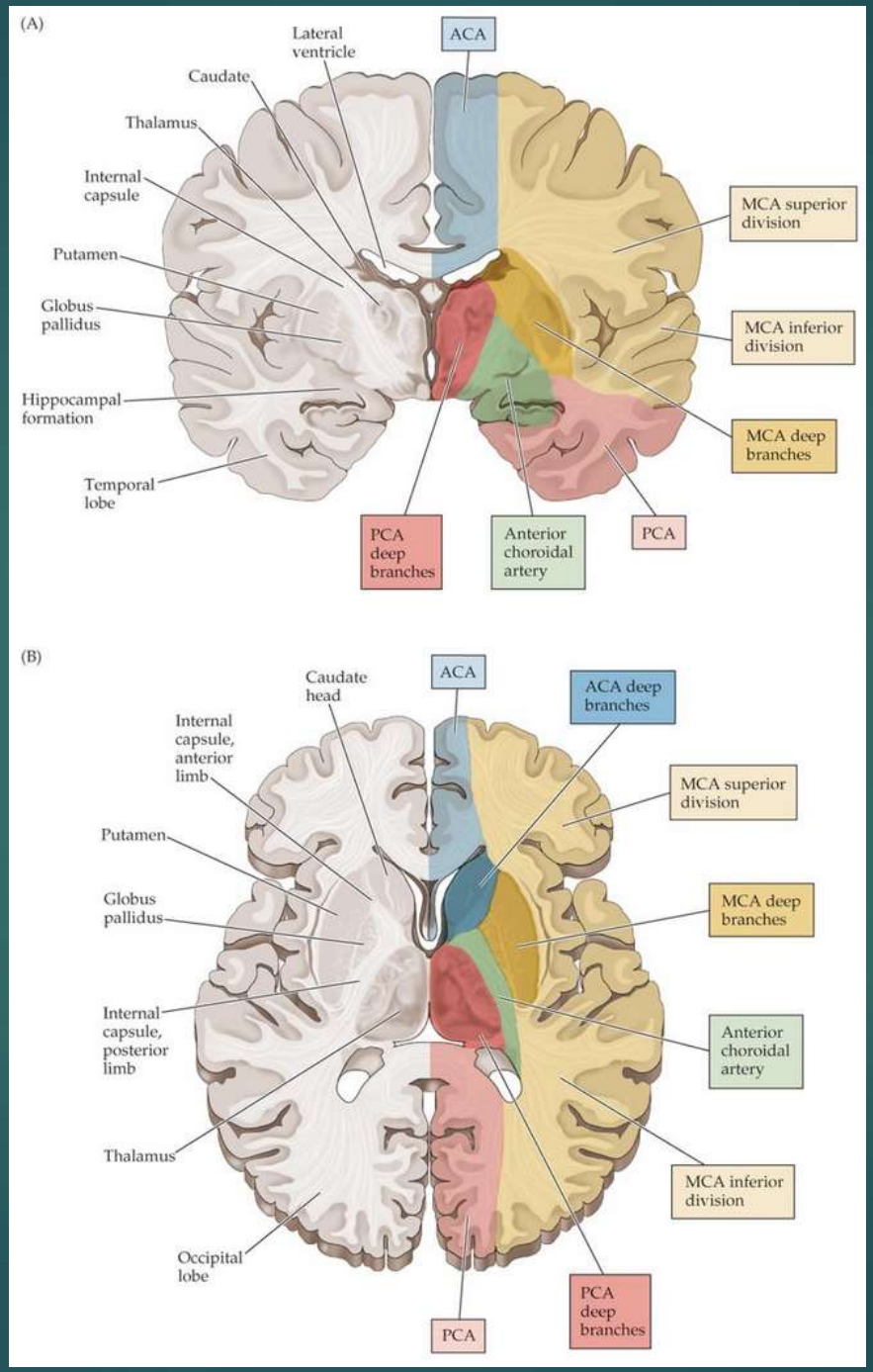
MCA

PCA

Artery Coverage Areas



Medial ACA & PCA Regions

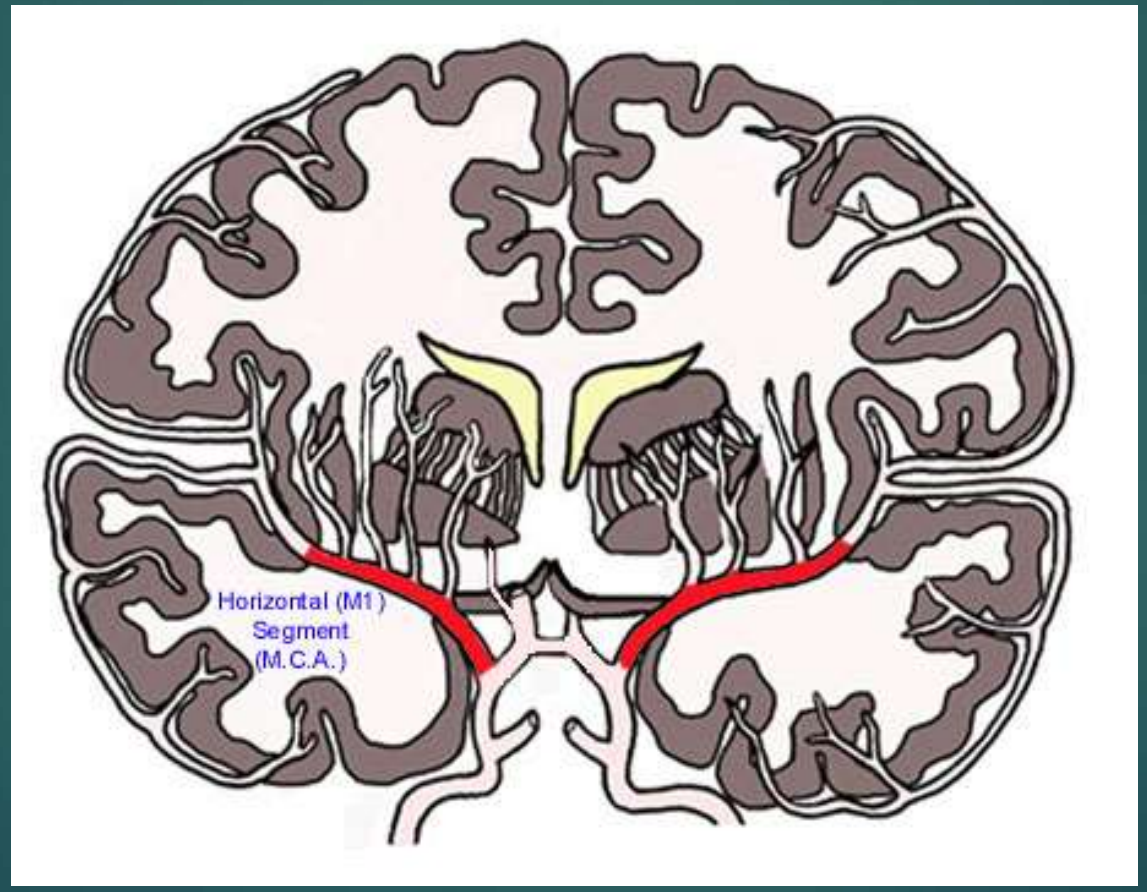


MCA Middle Cerebral Artery

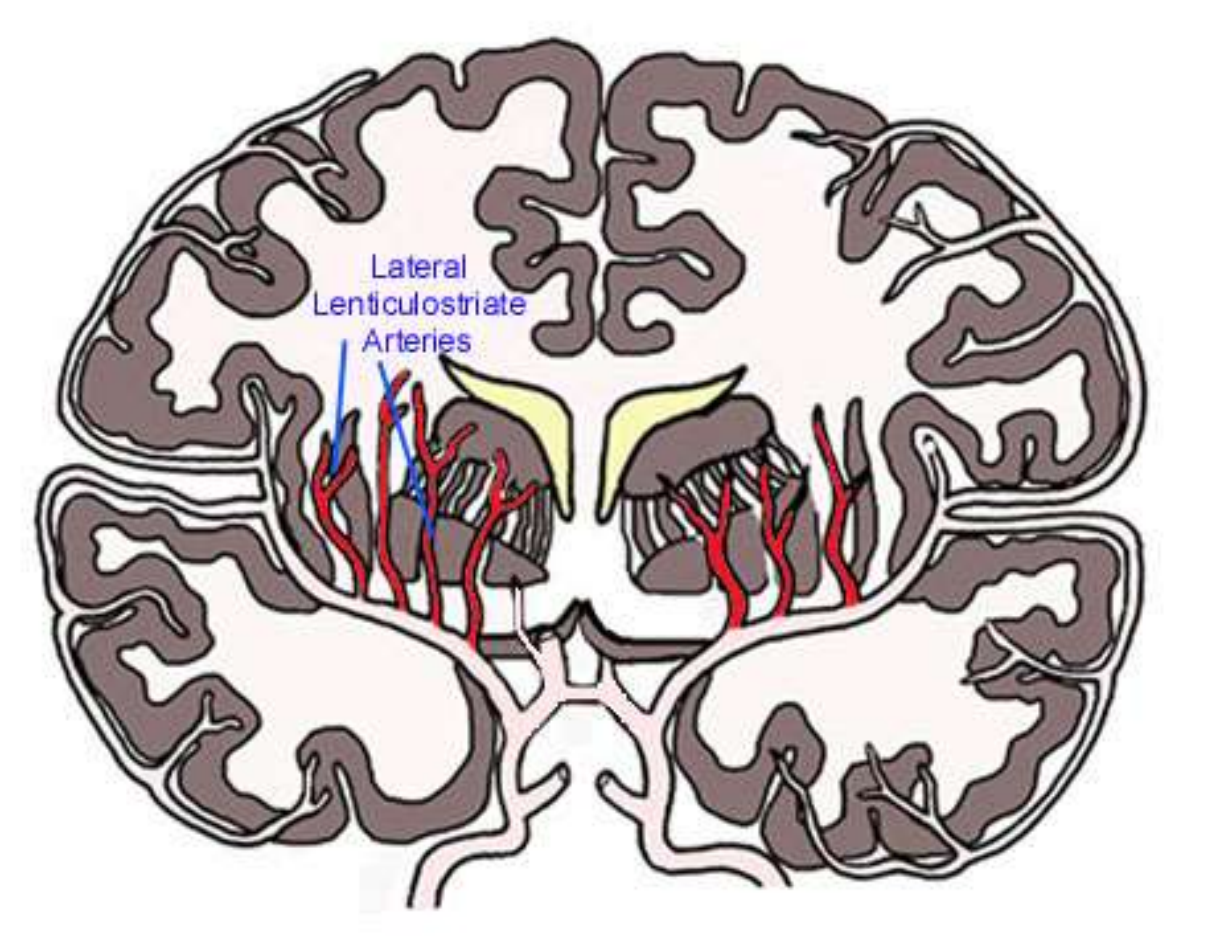
- 66% of strokes

- Lateral lenticulostriates (BG)
  - Superior Interior Capsule
  - Putamen, lateral GP, rest of Caudate
  - Corona radiata
- Major Hemispheric branches

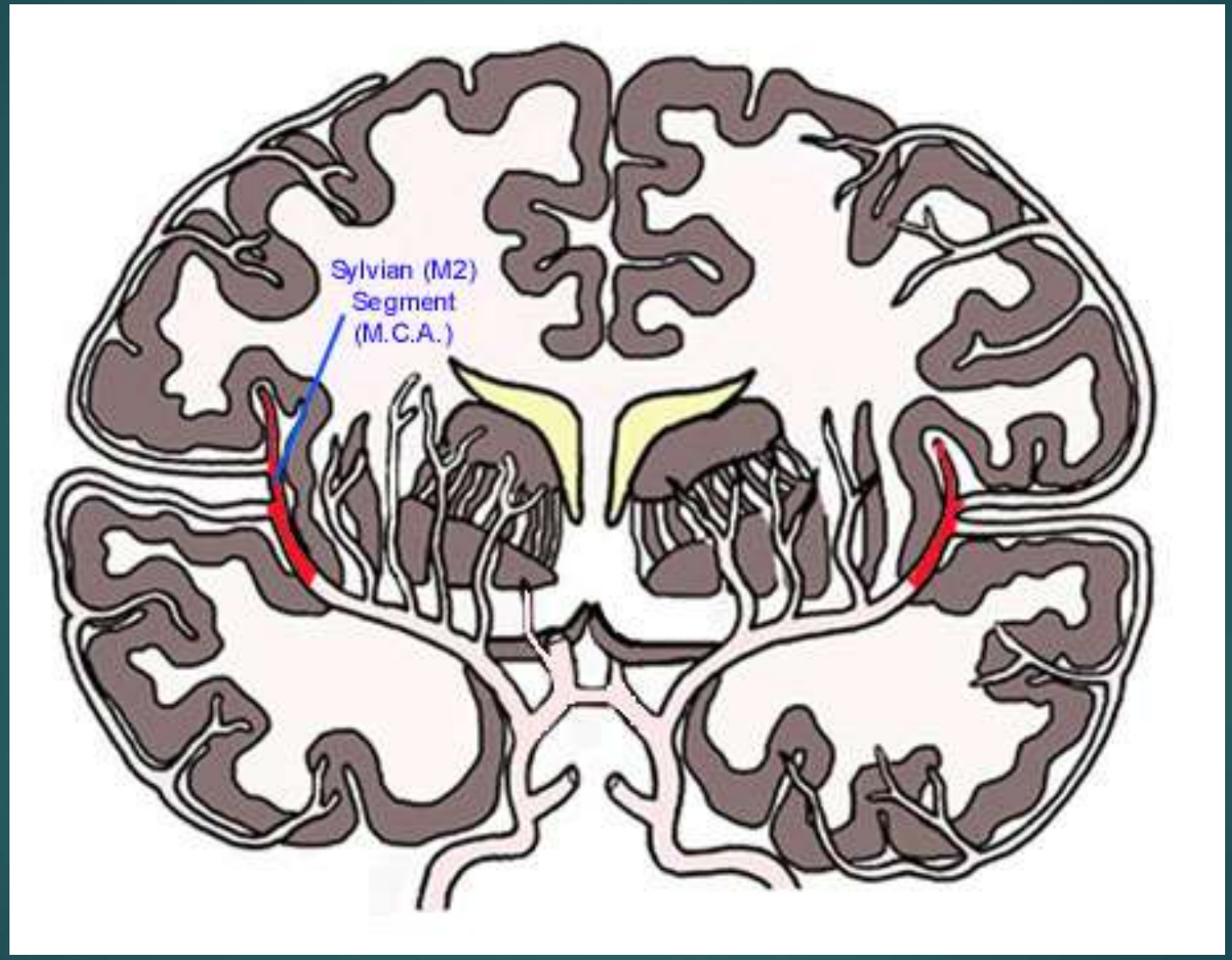
MCA - horizontal segment



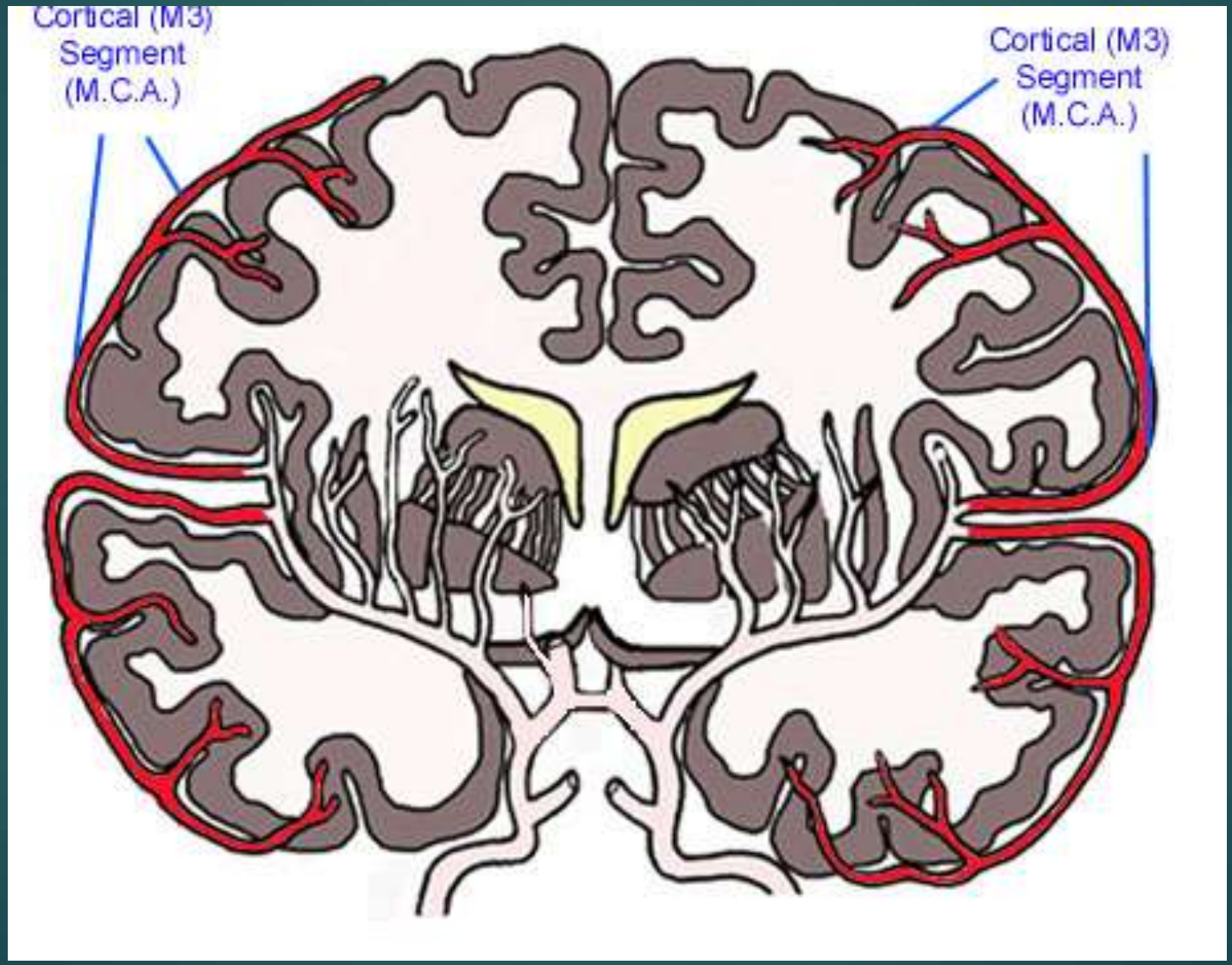
MCA – lateral lenticulostriate arteries (basal ganglia)



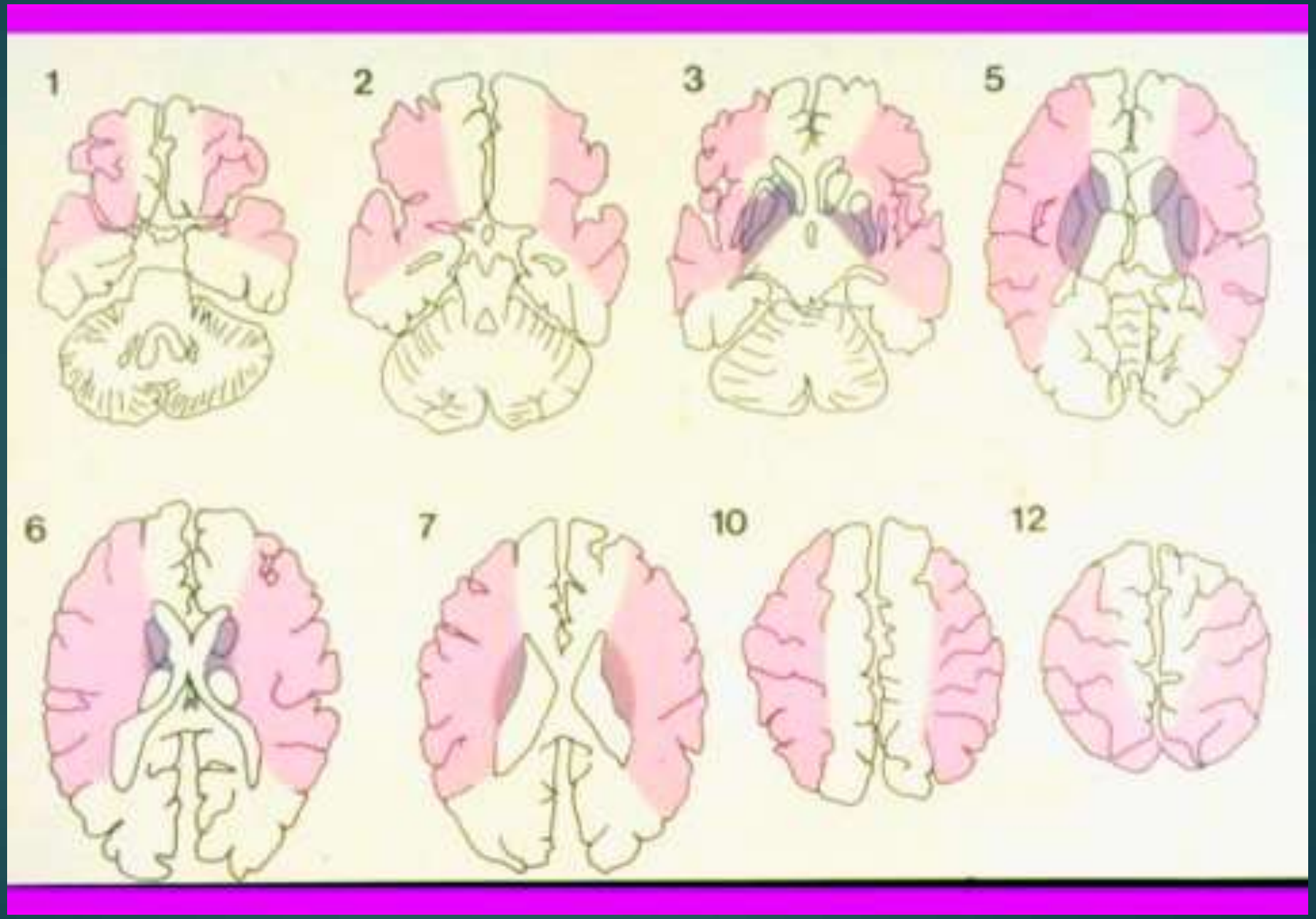
MCA – Sylvian segment



MCA - cortical segments



MCA



MCA

- MCA strokes are the most common
- Either Hemisphere:
  - Contralateral hemiparesis (motor weakness)/hemisensory loss
  - Face & arm > leg
  - Homonymous Hemianopsia (visual neglect)
    - Extinction to bilateral simultaneous stimulation
    - More common in right hemisphere strokes, producing left visual neglect
    - Hemi-neglect can be in all sensory domains acutely, then improves to 1 domain

Left MCA

- Dominant Hemisphere
  - Aphasia (esp. acutely): fluency, confrontation naming, repetition, comprehension, reading, writing
  - Visuoconstructional deficits (ok gestalt, poor details)
  - Memory impairments for verbal material
  - Gerstmann's syndrome (finger agnosia, acalculia, agraphia, R-L confusion)
  - Executive functioning (dorsolateral FL deficits if large superior MCA)
  - Motor apraxia

Right MCA

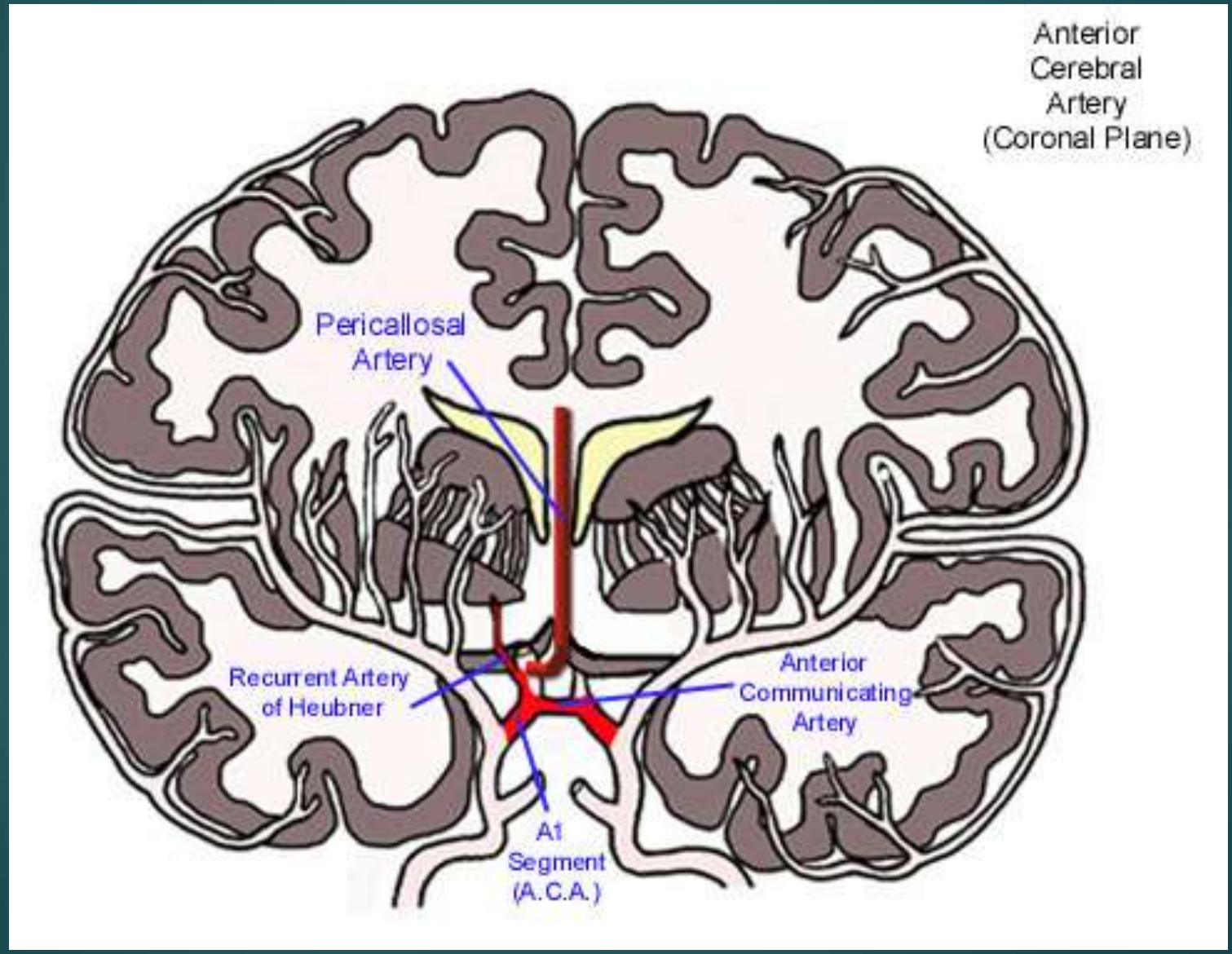
- Non Dominant Hemisphere
  - Acute confusional state
  - Left hemi-neglect (left side of space)
  - Agnosia
  - Visuoconstructional deficits (loss of gestalt, ok details)
  - Constructional apraxia (inability or difficulty to build, assemble, or draw objects)
  - Aprosodia (inability to convey or interpret emotional prosody)
  - Dressing apraxia
  - Visual memory deficits
  - Executive dysfunction

ACA - Anterior Cerebral Artery

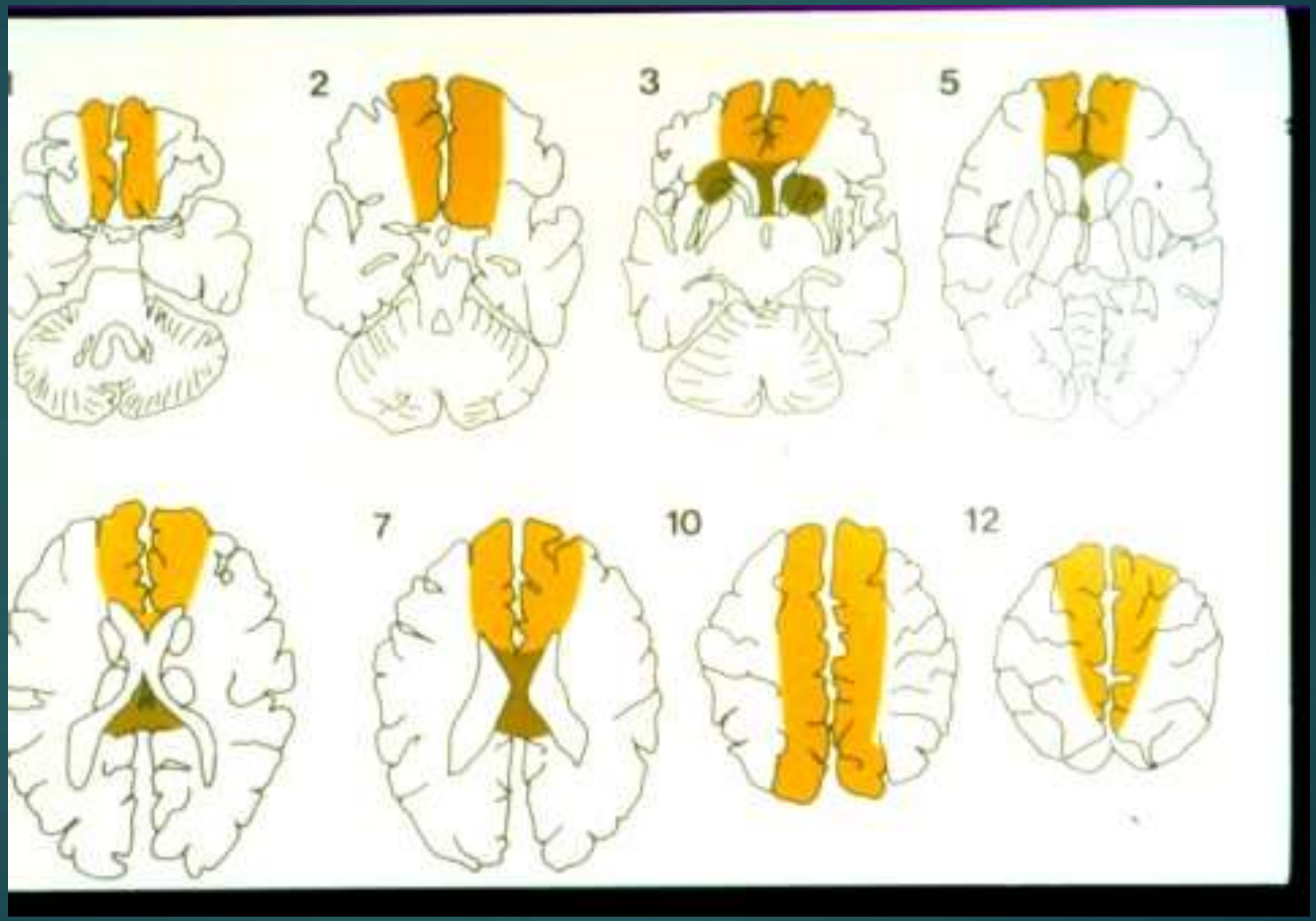
- 5% of Strokes (via occlusion or ACoA aneurysm)
- Often personality changes

- Medial Lenticulostriates (BG)
  - Anterior IC, Caudate Head (RAH)
  - Putamen and GP
  - Portions of Hypothalamus and optic chiasm
- Pericallosal branches
  - Corpus callosum
- Hemispheric branches
  - Medial frontal and parietal

ACA – recurrent arteries of Heubner & Pericallosal arteries



ACA



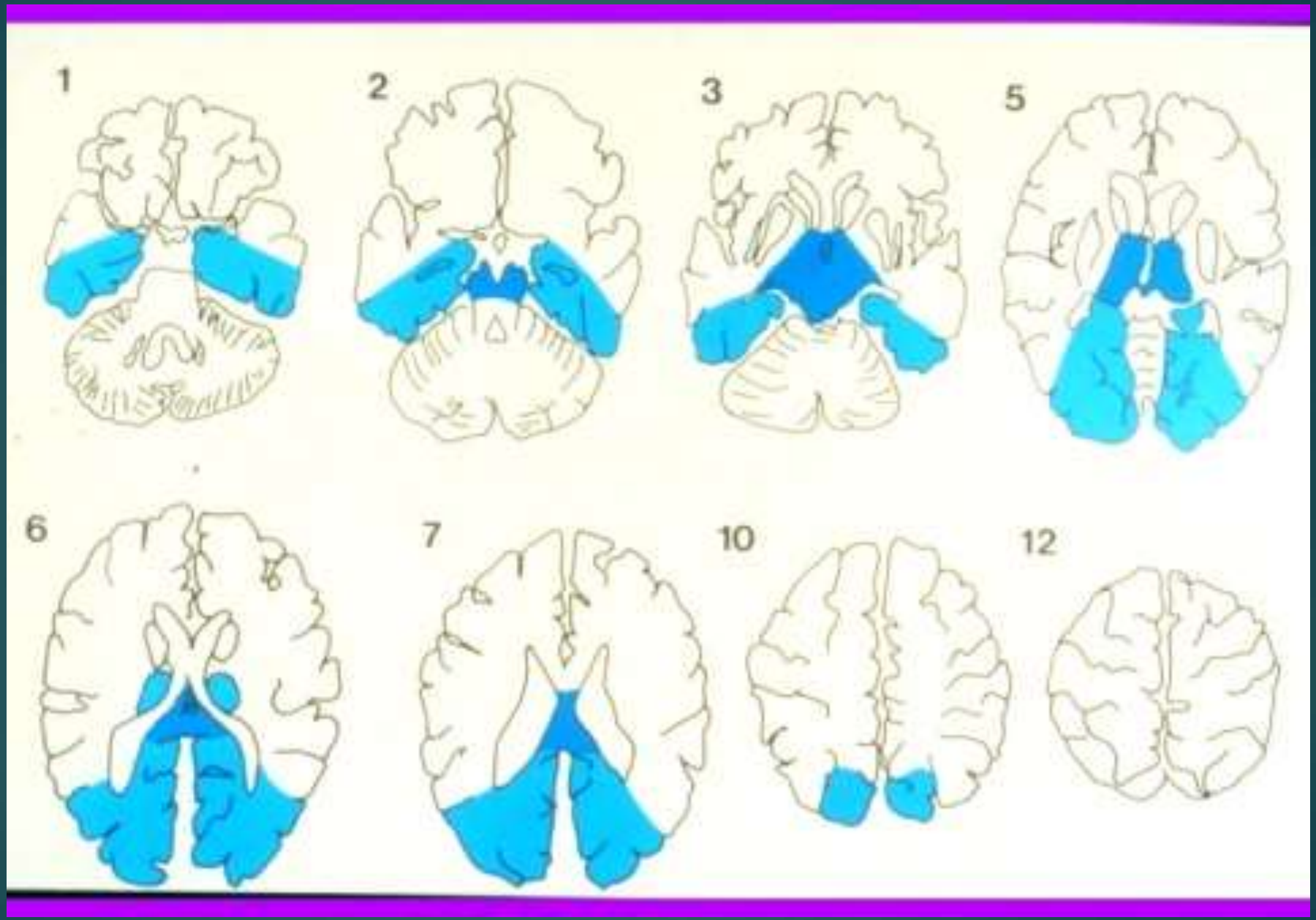
ACA deficits

- Contralateral weakness of feet/legs with falls (if unilateral)
- Urinary incontinence (if bilateral)
- Apathy, abulia (diminished motivation), akinetic mutism
- Lack of spontaneous speech (mute with damage to both medial frontal lobes)
  - Left ACA: expressive language deficits (phonemic fluency)
  - Right ACA: expressive aprosodies, poor social/emotional insight
- Executive dysfunction (deficits in retrieval strategies, false +s, prospective memory, divided attention/PASAT); behavioral disinhibition
- ACoA aneurysm (often bilateral damage): memory deficits, mutism, apathy, EF deficits
- 54% have NP deficits after aneurysm repair

PCA - Posterior Cerebral Artery

- 15% of Strokes
- Midbrain and Thalamic perforators
- Hemispheric branches
  - Posterior Choroidal
    - Choroid Plexus and Pineal gland
  - Cortical branches
    - Inferior temporal, parietal occipital, calcarine

PCA



PCA

Distal

- Contralateral sensory deficit of hands/arms (light touch, vibration, position)
- Unilateral: contralateral visual field deficit (hemianopsia); visoconstructional deficits very common
  - Left: receptive language (transcortical sensory aphasia – intact repetition), alexia without agraphia, ideomotor apraxia, Gerstmann's syndrome, verbal memory encoding, VS (loss of details),
  - Right: VS deficits (loss of gestalt), hemi-neglect common, receptive aprosodies, visual memory, prosopagnosia, color anomia
  - Behavioral: irritability, distractibility, agitation, psychosis
- Bilateral: Cortical blindness (deny their blindness), memory loss

Proximal (top of the basilar)

- Thalamic sensory deficits & pain syndromes; Impaired arousal; Extraoccular palsies

NP Rules of thumb

- Need to quickly identify aphasia, hemi-neglect, hemiparesis.
- Don’t repeatedly request a patient attempt tasks where failure is likely (motor tasks for hemi-paresis patient)
- If testing in acute or subacute period, will need to accommodate NP tests (place material in right hemispace for pts with left visual neglect)
- Attempt to identify strengths and weaknesses.

Ischemic vs Hemorrhagic Strokes

- Ischemic strokes follow cerebral vascular neuroanatomic territory
- Hemorrhagic strokes are more diffuse, often involving several different vascular territories; vary more widely than Ischemic strokes
- Subdural hemorrhages don’t involve center of brain; NP deficits can be minimal

Neuropsych Assessment 2

- Always assess memory and attention
- Assess IQ if possible, if not get an estimate based on educational/vocational history
- Then evaluate specific abilities based on lesion location/vascular distribution as determined by CT or MRI

Evaluation of Left-Hemisphere strokes

- Thoroughly evaluate language abilities
- If patient is aphasic:

  If aphasia is severe, first test the reliability of yes/no responses. If yes/no is unreliable, patient is ***not testable***.

  Can use multiple choice or yes/no format when interviewing

  Use gestures and facial expression to convey test instructions if necessary.

Evaluation of Left-Hemisphere strokes 2

- Use only nonverbal tests to estimate premorbid IQ

- Concentrate on nonverbal tests such as WAIS or WASI Performance subtests, visual memory tests, WCST (if pt higher functioning)

- Also evaluate language functioning

  NAB Language module or Cognistat language subtests

Evaluation of Right-Hemisphere strokes

- Evaluation of right-hemisphere strokes:
  - Evaluate visual-spatial abilities carefully
  - Look for left visual neglect
- Evaluation of occipital strokes:
  - Look for visual field cuts, impaired ability to recognize objects by sight
- Evaluation of frontal strokes:
  - Evaluate executive functions carefully, language and motor abilities

TMT-B

- A 1-SD increase in TMT-B time is associated with a higher risk for brain infarction.

- The risk of brain infarction is more than 3-fold higher if TMT-B is in the range of 146-240 seconds

Miscellaneous details

- Evaluate areas of strength as well as weakness.
- Sometimes necessary to adjust standard test administration to accommodate patient's disabilities (e.g., hemiplegia)
- Interpret test results qualitatively as well as quantitatively

Miscellaneous tips 2

- Evaluate emotional changes
- Refer for medication evaluation as needed
- Include patient's family
  - education, support, behavioral management strategies

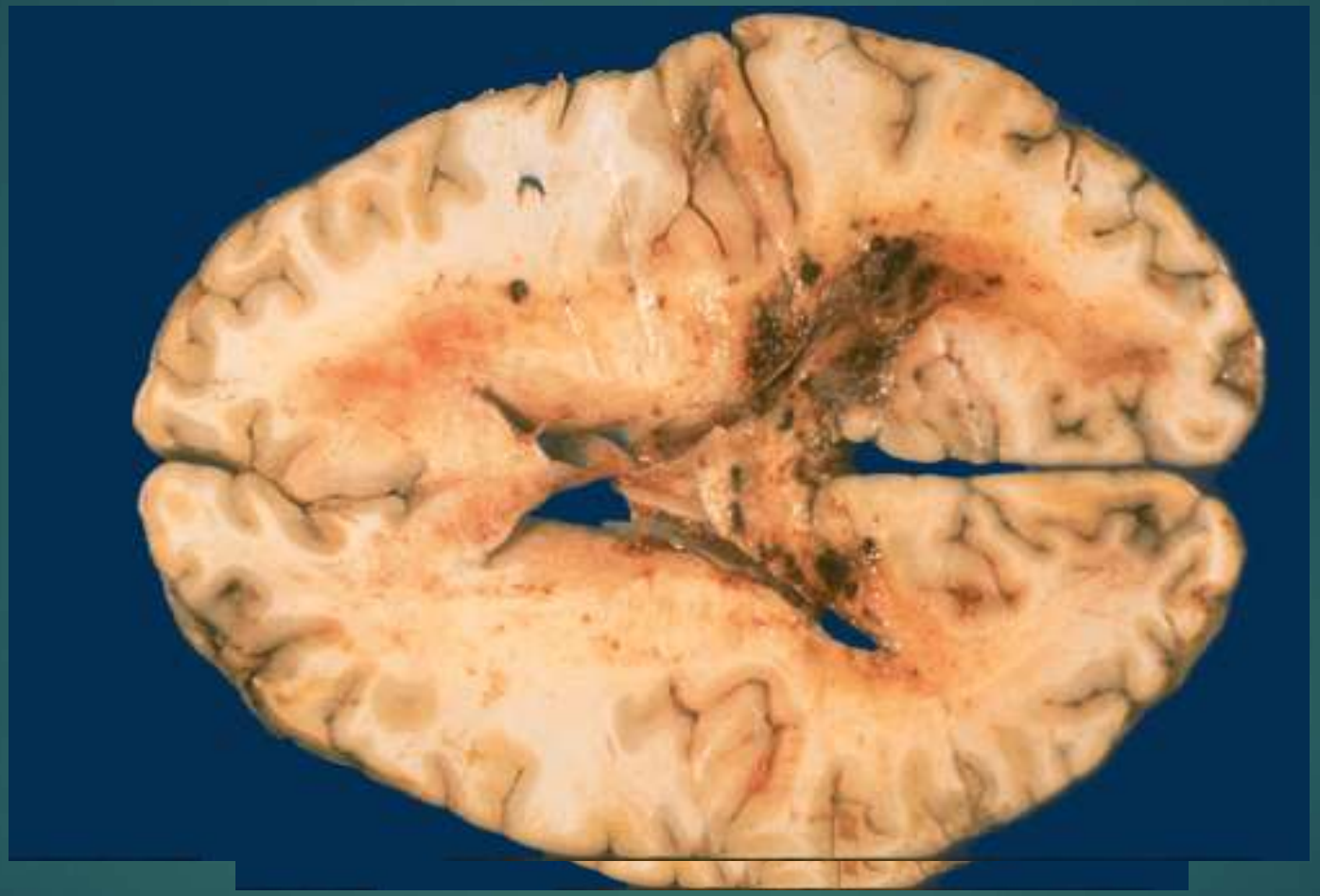
Cardiovascular surgery

- CV surgeries in US adults aged 65+ annually
  - 200,000 coronary artery bypass graft (CABG) surgeries,
  - 50,000 carotid revascularizations,
  - 50,000 cardiac valve replacements or repairs,
  - 10,000 catheter ablations for atrial fibrillation

Cardiovascular Disease

- Leading cause of morbidity and mortality in US
  - 41% of all deaths (Kaiser now: CA > CV)
  - 60 million have CVD: $128 billion
  - 600 T strokes per year:
    - leading cause of adult disability
    - 3rd leading cause of death
    - 3.9 million have had stroke

Cerebrovascular disease



Cardiovascular Disease: Types

- Hypertension: 50 million in US, =>140/90
- Coronary artery disease (CAD): 12 million, ½ of CV deaths, primary cause of sudden death
- Cerebrovascular disease
- Cardiomyopathy: 2nd major cause of sudden death
- Peripheral Vascular Disease: 3.5 million (aneurysm, and peripheral arterial disease (PAD)
- Congenital Heart Disease (CHD)
- Rheumatic Heart Disease
- Valvular Heart Disease
- Congestive Heart Failure (CHF): 4.6 million (heart can't pump enough blood to meet your body's needs)
- Cardiac Arrhythmias

Cardiomyopathy

- Cardiomyopathy = chronic diseases of the heart muscle causing cardiac dysfunction. In cardiomyopathy, the heart muscle becomes enlarged, thick, or rigid. Progressive symptoms of heart failure
- As cardiomyopathy worsens, the heart becomes weaker. It's less able to pump blood through the body and maintain a normal electrical rhythm. This can lead to heart failure or arrhythmia. In turn, heart failure can cause fluid to build up in the lungs, ankles, feet, legs, or abdomen.
- Main cause of cardiovascular morbidity and mortality in both children and adults and are a frequent indication for cardiac transplantation
- 26,000 deaths each year in the United States are caused by cardiomyopathy. 2nd only to CAD as cause of sudden death

Heart Failure → Cognitive Deficit

- Overall, patients with HF score lower than controls on 74% cognitive tests.

- 46% of the HF patients: rated as having mild to severe cognitive impairment, compared to a 16 percent rate of mild impairment in controls.

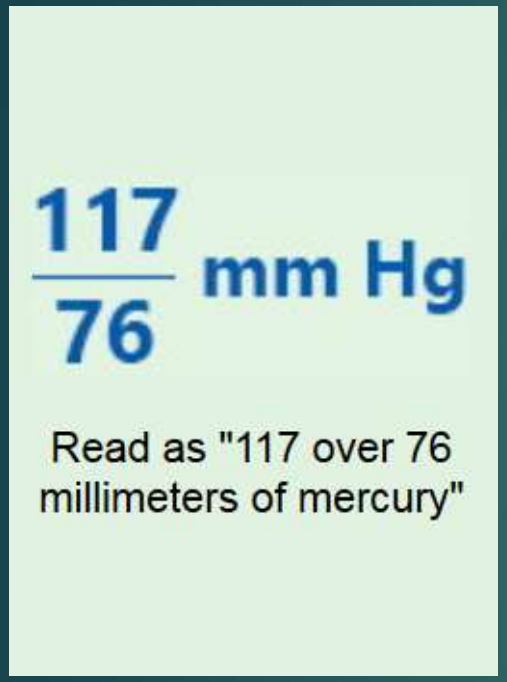
- Memory problems, especially short-term memory, were the most common type of cognitive deficit.
- The risk of cognitive impairment was more than four times higher in the HF group. The rate, types, and severity of cognitive impairment in this group of patients living with HF were similar to those seen in patients with end-stage HF awaiting heart transplantation.

M. Sauve, Journal of Cardiac of Cardiac Failure, 2009

Hypertension: curse of the brain

- Major precursor of most types of Stroke
- Can cause hemorrhagic (bleed) or ischemic (Ox blockage) changes
- Can be associated with periventricular white matter changes (WH+) on CT or MRI
- Causes auto-dysregulation of blood vessels

Blood Pressure



Systolic

The top number, which is also the higher of the two numbers, measures the pressure in the arteries when the heart beats (when the heart muscle contracts).

Diastolic

The bottom number, which is also the lower of the two numbers, measures the pressure in the arteries between heartbeats (when the heart muscle is resting between beats and refilling with blood).

New = normal blood pressure as below 120/80 mm Hg and elevated blood pressure as 120 to 129 mm Hg systolic with a diastolic pressure below 80 mm Hg.

American Heart Association: new = 46% of U.S. adults have HTN

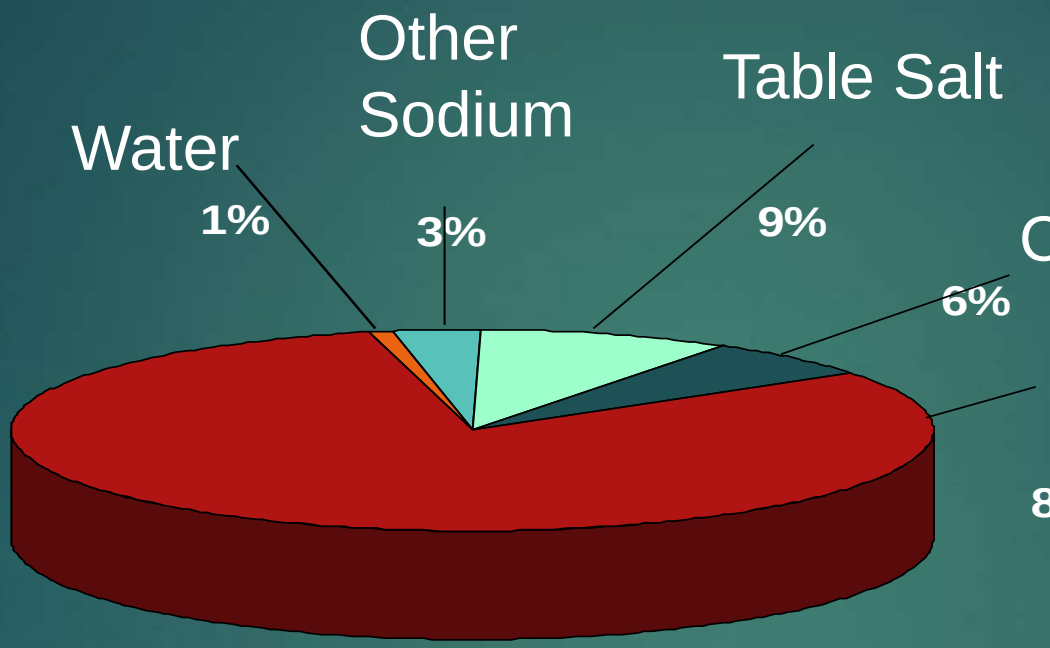
Blood Pressure Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than **120**	and	less than **80**
Prehypertension	**120 – 139**	or	**80 – 89**
High Blood Pressure (Hypertension) Stage 1	New = 130-139 **140 – 159**	or	**90 – 99**
High Blood Pressure (Hypertension) Stage 2	New = 140/90 **160** or higher	or	**100** or higher
Hypertensive Crisis (Emergency care needed)	Higher than **180**	or	Higher than **110**

New guidelines for 65+: start treatment for patients who have persistent systolic blood pressure at or above 150 mm Hg to achieve a target of less than 150 mm Hg

Prehypertension & Prediabetes

- Stage 1 hypertension is defined as 130 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic, and stage 2 hypertension as 140/90 mm Hg or higher (the old definition of hypertension). What is now called stage 1 hypertension was previously labeled “prehypertension” —
- Prehypertension, defined as
  - a blood pressure between 120 to 139 over 80 to 89 mm Hg
- Prediabetes, blood sugar between 100 and 125 mg/dL
- are two very early warning signs of potential for future heart attack or stroke.

Sources of Dietary Salt - risk factor for HTN



Processed Food:
High in salt, sugar, transfats: bacon, instant ramon, microwave popcorn, salami, frozen dinners

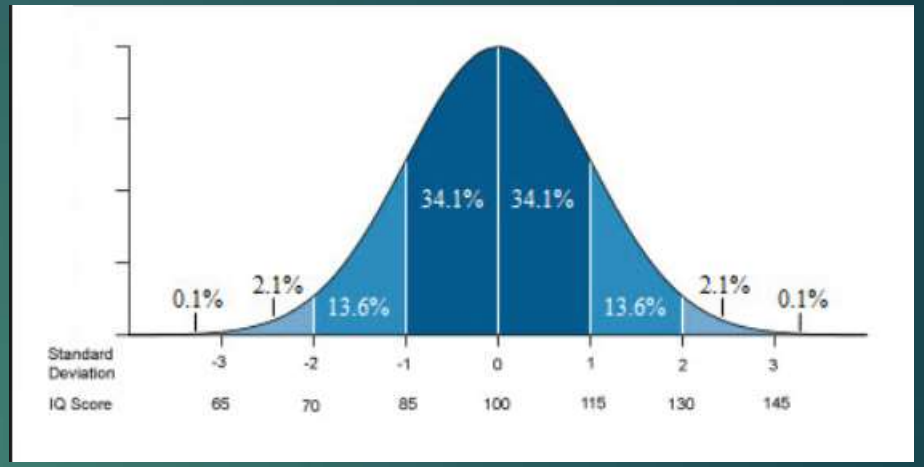
Source: James et al. The dominance of salt in manufactured food in the sodium intake of affluent societies. Lancet 1987;8530:426-428.

Hypertension and Cognitive Function

- > 140/90 = 50 million
- Essential HTN: unknown cause, 90-95%
- HTN is risk factor for atherogenesis, CHD, stroke
- Risk factors: male, African American
- 75% of all CHF; 35% of all Strokes due to HTN
- Neuropsychological Deficit: 1 s.d.↓
- Ask about HTN #s & medication compliance in all NP interviews

Hypertension and Cognitive Function 2

- Cognitive Deficit: 1 s.d.↓ = 15 points in IQ of 100

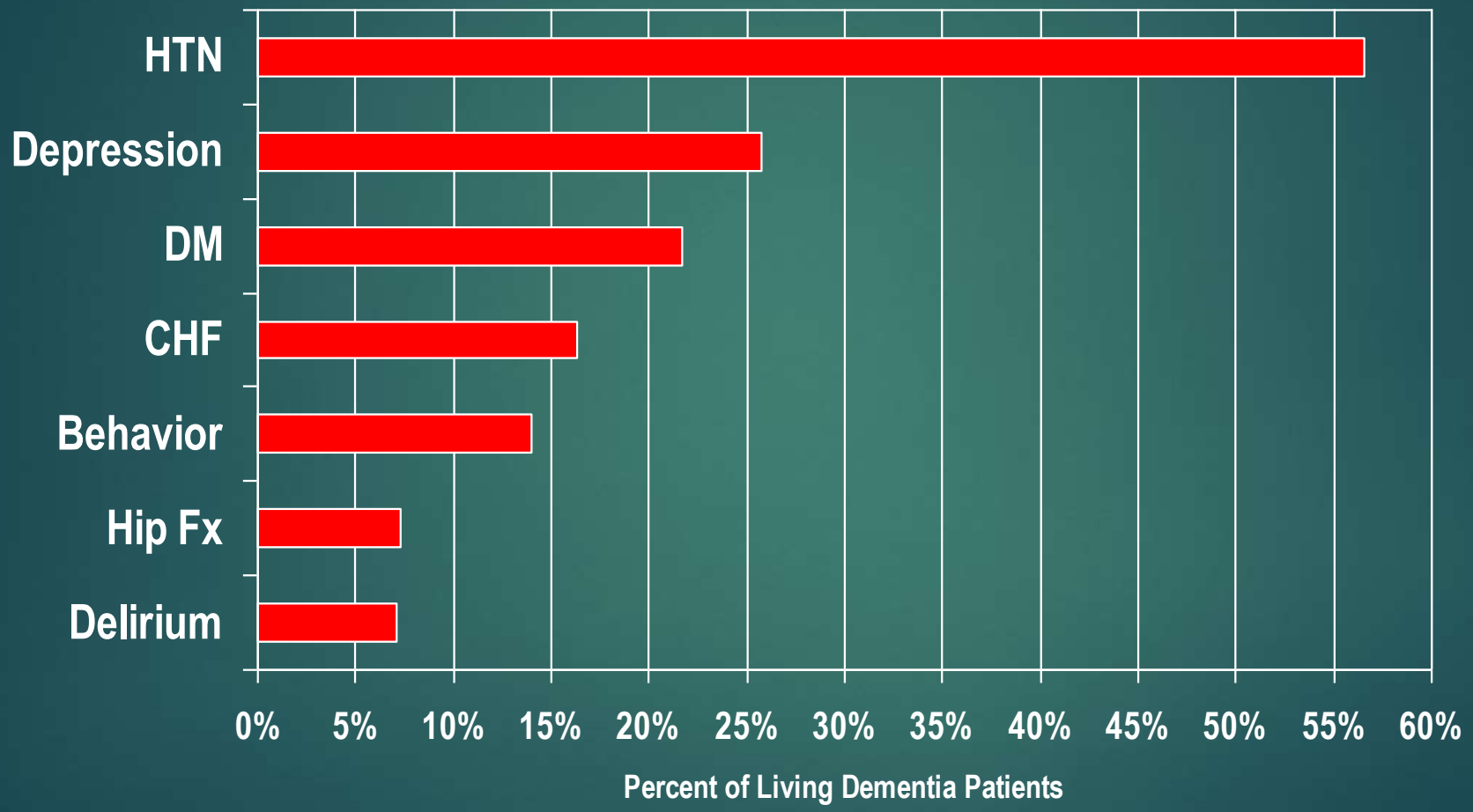


- Dose-response relationship between increasing HTN & cognitive functioning (as well as low BP)
- Memory, Attention, Executive Functioning (Problem Solving) ↓ ↓ ↓
- Persons with elevated blood pressure (BP) show dampened emotional responses to affect-laden stimuli.

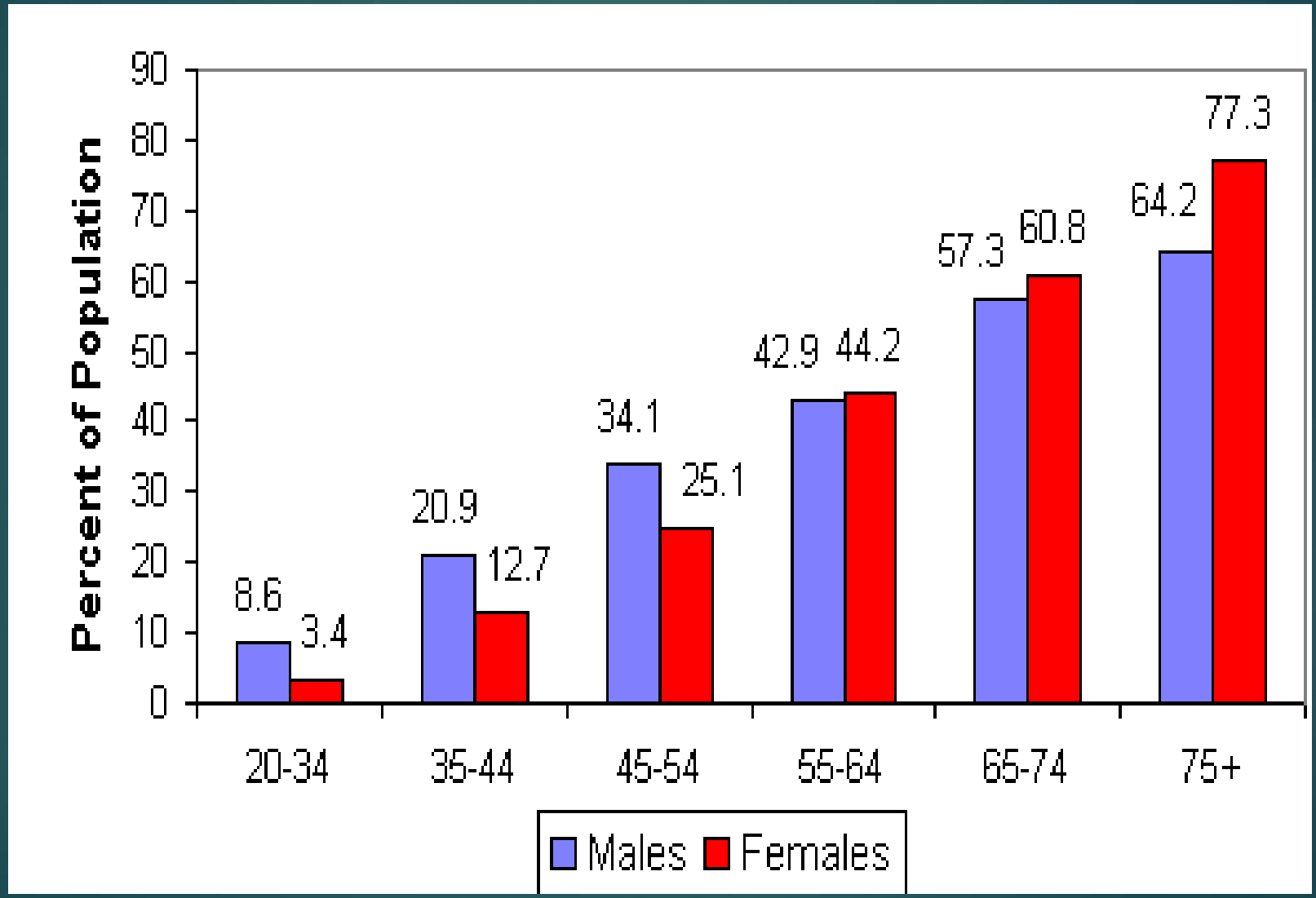
Hypertension and Cognitive Function 2

- Dose-response relationship between increasing HTN & cognitive functioning (as well as low BP)
- Memory, Attention, Executive↓
- Persons with elevated blood pressure (BP) show dampened emotional responses to affect-laden stimuli.
- Lowered average levels of NP functioning
  - Worse when younger onset
  - Chronicity worsens
  - Worse with DM

Co-Morbidities of Northern Cal KP Dementia Pts



Age and Increasing Hypertension



Hypertension and Cognitive Function 3

- Hypertension correlates:
  - CBF and glucose utilization decrease (in rats)
  - Structural effects: MRI hyperintensities in periventricular and deep white matter (reverses with TX)
  - More lacunar infarcts, atrophy, ventricular enlargement, carotid atherosclerosis
  - All related to neuropsychological decrease

Hypertension and Emotional Recognition

- Persons with elevated blood pressure (BP) show dampened emotional responses to affect-laden stimuli.

Hypertension & Bipolar Disorder

- Nearly half of patients hospitalized with bipolar disorder may suffer from hypertension,
- The younger a person is diagnosed with the psychiatric condition the more likely they are to develop high blood pressure
- Bipolar patients with high blood pressure suffered higher levels of mania.
- Both can be triggered by stress and are tied to the excretion of norepinephrine, a hormone affecting how the brain reacts to stress.
- Treat hypertension more aggressively in bipolar patients

Systolic Dysfunction can cause cognitive deficits

- Of 80 older adults, two-thirds of those with systolic dysfunction had evidence of memory impairment - affecting both their immediate and delayed memory. In contrast, only 21% of those patients with diastolic heart failure had memory-related cognitive impairment.

- Heart failure etiology likely contributes to the cognitive impairment patterns demonstrated in chronic heart failure patients

L. Bauer, 2010

Diastolic Blood Pressure & Cognitive Decline

- 19,836 participants (2003 to 2007); Diastolic BP (relaxing)
- Baseline relationships between BP components (systolic blood pressure [SBP], diastolic blood pressure [DBP] and impaired cognitive status (score of <=4 on 6-Item Screener)
- Higher Diastolic BP levels were associated with impaired cognitive status
- Increment of 10 mm Hg in DBP was associated with a 7% higher odds of cognitive impairment.

G. Tsivgoulis, 2009

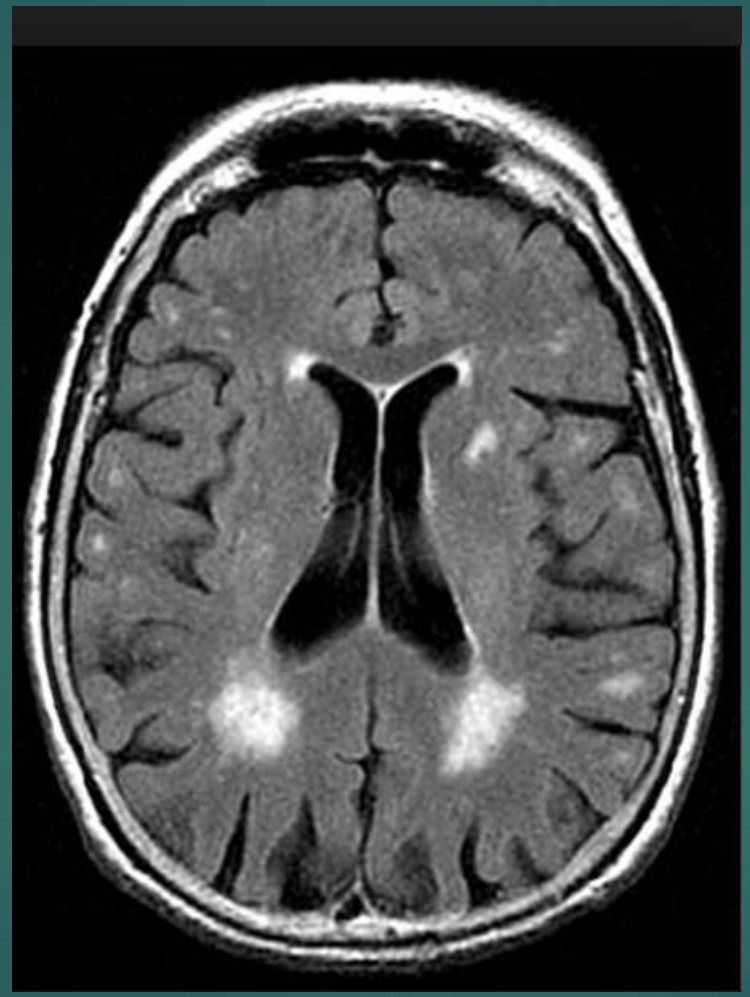
Good Cognitive Consequences of Antihypertensive Medications

- Untreated Hypertension: The Framingham Study: Untreated blood pressure level is inversely related to cognitive functioning: HTN →→ cognitive decline.

- Antihypertensive medication use →→ preservation of cognitive function in older Caucasian and African American adults.

- Antihypertensive use, (particularly diuretics, angiotensin-converting enzymes inhibitors, beta-blockers, and angiotensin receptor blockers), may be associated with a lower rate of cognitive decline (MMSE, Clock) in older adults, including those with AD.

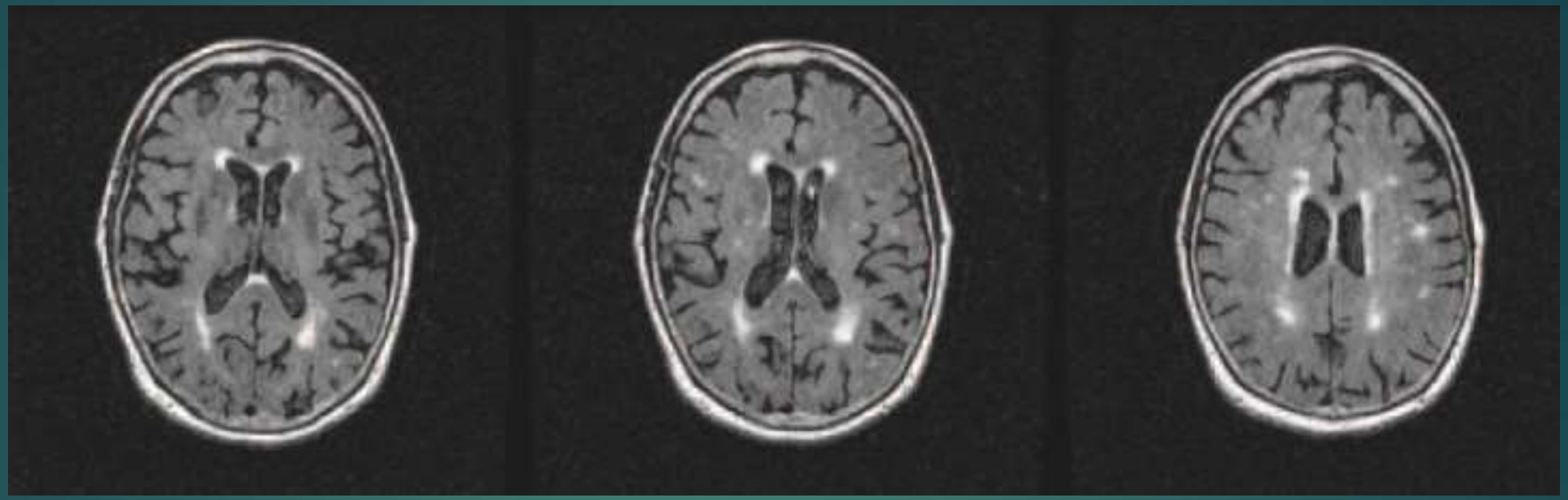
Vascular Periventricular Hyperintensities



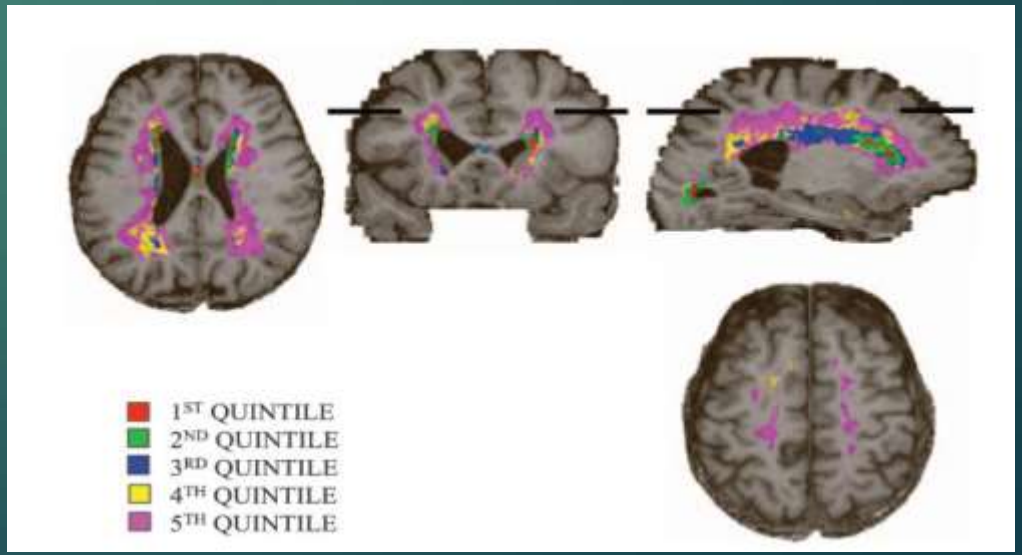
CVD and White Matter Hyperintensities (WMH)

- CVD (HTN, midlife abdominal girt, etc.) causes brain atrophy and WMH+ (white matter hyperintensities)
- Dysregulation of autoregulatory control of CV system is cause of WMH+, not microinfarcts
- HTN creates stiffer blood vessels; hypoperfusion when stand up (toilet flush effect)
- WMH+ doubles mortality risk

White Matter Hyperintensities on MRIs: Small blood vessel damage

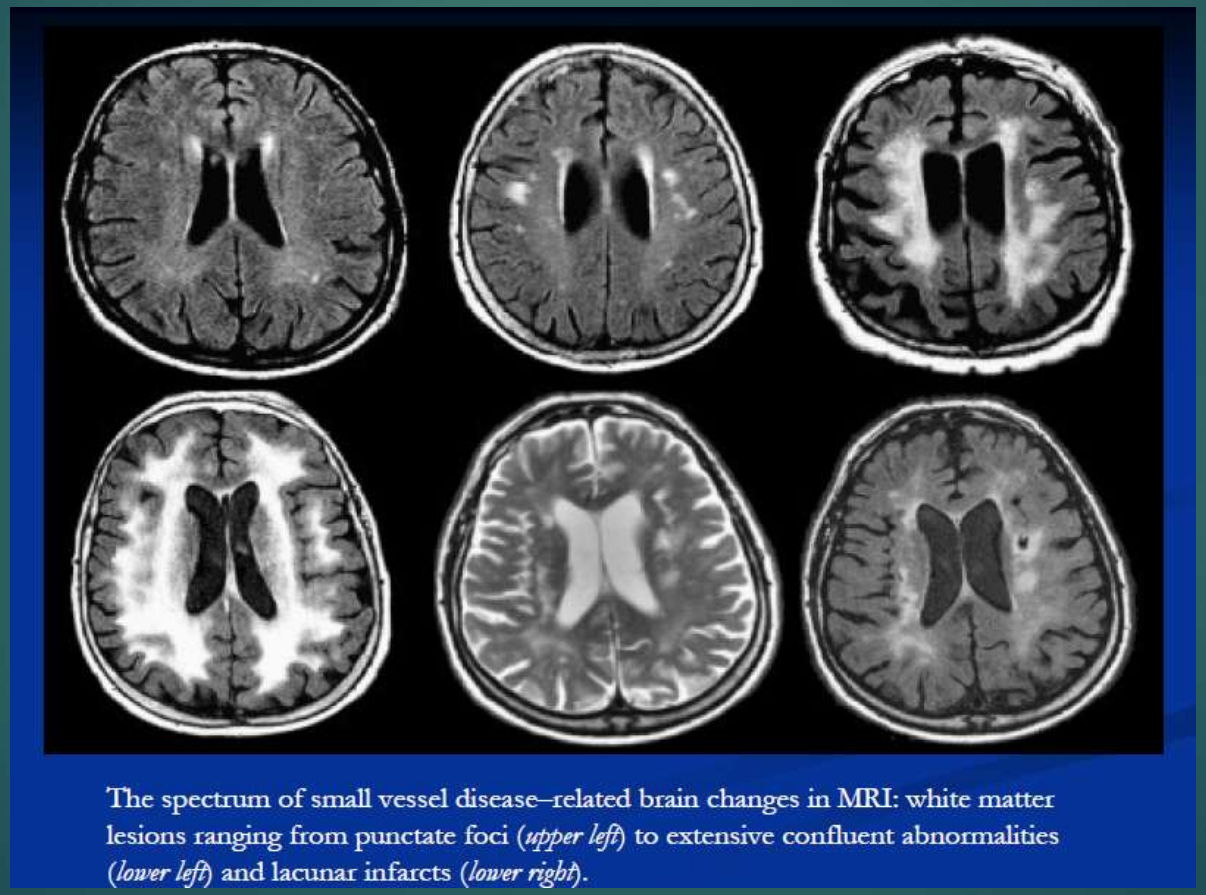


A single vascular white matter watershed area extending between 3 and 13 mm from the ventricular surface.
Strong associations between vascular risk factors and vascular disease when WMH volumes are extensive.



DeCarli, et al., 2005

Mild to Extensive Vascular Hyperintensities: Slower Processing Speed



The spectrum of small vessel disease–related brain changes in MRI: white matter lesions ranging from punctate foci (*upper left*) to extensive confluent abnormalities (*lower left*) and lacunar infarcts (*lower right*).

Hyperintensities & AD

- Participants whose white matter hyperintensities were significantly above average at the beginning of the study lost more points each year in cognitive testing than those whose white matter hyperintensities were average at baseline.

- Presence of white matter hyperintensities and MCI or Alzheimer's disease together added up to even faster and steeper cognitive decline.

Owen Carmichael, 2010

Hyperintensities 2

- Extent of white matter hyperintensities was associated with greater subsequent declines in global cognition over a one-year period.

- White matter disease may be an important predictor of subsequent global cognitive change.

Serum Cholesterol and Cognitive Functioning

- Hypercholesterolemia (hyperlipidemia) leads to carotid atherosclerosis, stroke, and AD and diminished cognitive functioning, esp. in elderly (98 Million have >200 mg/dl)

- Lower cholesterol related to better IQ performance and grades, memory, processing speed, Digit Symbol, Block Design; may be a curvilinear relation (best in middle)

Serum Cholesterol and Cognitive Functioning 2

- APO-E = cholesterol protein: risk of AD onset
- Cholesterol medication lowers # of ischemic strokes (not lacunar strokes, or vascular dementia)
- Cholesterol-lowering drugs prevent large ischemic strokes

Triglycerides

- In recent study, triglycerides were best predictor of future strokes
- Better than cholesterol level and HDL
- Triglycerides are the main constituents of vegetable oil (typically more unsaturated) and animal fats (typically more saturated)
- Diets high in carbohydrates can increase triglyceride levels.
- Normal = <150 mg/dl

Retinopathy & Cognitive Decline

- Link between retinopathy (changes in the blood vessels of the retina), cognitive performance over time, and white matter hyperintensities and lacunar infarcts in the basal ganglia.
- Presence of retinopathy was associated with poorer 3MSE scores over a 10-year follow-up period and greater ischemic volumes in the total brain and the parietal lobe
- Retinopathy as a marker of small vessel disease is a risk factor for cerebrovascular disease that may influence cognitive performance and related brain changes.

M. Haan, et al., 2012

What is ‘metabolic syndrome’?

- 1 Abdominal obesity (fat belly)
- 2 Impaired glucose metabolism (diabetes, pre-diabetes)
- 3 High “bad” cholesterol (LDL) or low “good” cholesterol (HDL)
- 4 High blood pressure

- Almost all cases of adult onset diabetes begin as Metabolic Syndrome
- Each metabolic syndrome factor independently increases stroke risk;
- Having all 4 doubles dementia risk
- Each metabolic syndrome factor independently increases stroke risk
- And increases the risk of cognitive impairment

Each metabolic syndrome factor independently increases stroke risk

- Abdominal obesity :
  - Higher waist-hip ratio increases risk 2-3 times
- Diabetes :
  - Twice the risk of stroke versus no diabetes
- Cholesterol
  - Related to atherosclerosis
- High blood pressure
  - Directly related to degree of BP elevation

Metabolic syndrome increases the risk of cognitive impairment

- Study of 4,895 women in their 60's
  - Risk increased by 23% for every factor present

- Kaiser study of over 8,000 people
  - Risk increased by 20-40% for smoking, diabetes, cholesterol, blood pressure
  - Having all 4 factors doubles risk of dementia

HDL and Cognitive Decline in normals

- HDL (good cholesterol) is positively correlated with grey matter volume in the temporal lobes.

- A significant association between HDL and the Brief Visuospatial Memory Test, COWAT

- Those with decreased levels of HDL cholesterol may be experiencing cognitive changes and GM reductions in regions associated with neurodegenerative disease.

M. Ward, et al., 2010

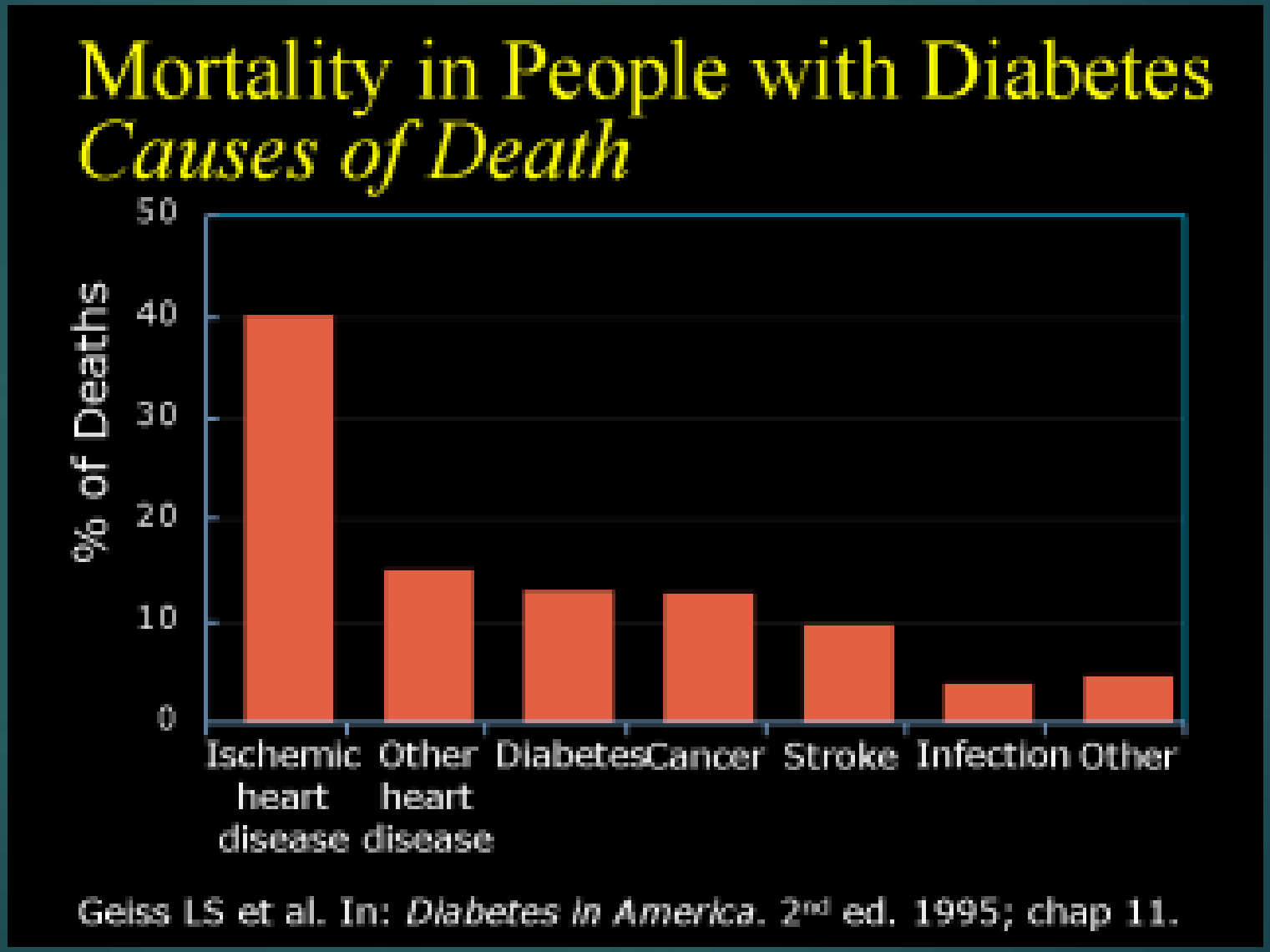
Cigarette smoking: stroke and dementia

- Cigarettes are lethal: 400,000 deaths per year
- Increases stroke risk by worsening atherosclerosis (blood vessel narrowing)
  - Even with passive (“second hand”) exposure
- Five times faster decline in cognition/dementia in smokers compared to non-smokers
  - Study of 9,000 adults over age 65
- Lothian Study: Not reverse causation for smoking: lower IQ do more smoking, have harder time giving it up, and end up with lower cognition

Diabetes-Associated Cognitive Dysfunction

- DM and CVD intertwined
- DM adults have 2x rate of normals of:
  - Hypertension
  - Dyslipidemia
  - Heart disease
  - Stroke
- NP deficits related to DM (independent of CVD)

Diabetes: Ischemic Heart Disease is primary cause of death



Diabetes M**ellitus**

- Type 1: (insulin-dependent, juvenile onset)
  - Early onset
  - Autoimmune destruction of pancreatic cells
  - When pancreatic beta cells are unable to maintain adequate insulin secretion to prevent hyperglycemia (high blood sugar)

- Type 2: (non-insulin dependent)
  - Development of insulin resistance
  - Average onset = age 60

Type 1 DM: child and adolescent

- Onset before age 5 and 1 or more severe hypoglycemic events: 25% decline in NP
  - Attention ↓
  - Developmental delays on Vocabulary & Block Design

- Onset age 6-14: do not have NP deficits, except somewhat lower scores on achievement tests
- Severe hypoglycemia:
  - Attention ↓
  - Memory ↓
  - Visual spatial ↓
  - EEG abnormalities

Type 1 DM: adult

- Relatively subtle cognitive impairment if any
- Deficits related to peripheral neuropathy and chronic hyperglycemia
- Retinopathy
- Peripheral neuropathy: strong relationship with cognitive ↓
- If poorly controlled: mild-moderate diabetic encephalopathy (demyelinization):
  - Processing Speed ↓ ↓
  - Attention ↓
  - Memory ↓
  - Visual spatial ↓
  - Executive ↓ (esp. if 15 years +)

Type 1 DM: adult 2

- Recurrent hypoglycemia:
  - Single profound hypoglycemic episode can produce brain damage
  - Increased cortical atrophy
  - No NP deficits (in longitudinal studies of 13-39 y)
  - NP deficits (in cross sectional studies):
    - Visual spatial ↓
    - Psychomotor slowing
    - Fluid IQ ↓
    - Decision making ↓

Obesity + Type 2 Diabetes & Cognition

- 18 obese adolescents with type 2 diabetes and compared them to equally obese adolescents from the same socioeconomic and ethnic background but without evidence of marked insulin resistance or pre-diabetes.
- Significant reductions in performance on tests that measure overall intellectual functioning, memory, and spelling, which could affect their school performance, but also had clear abnormalities in the integrity of the white matter in their brains.

EF and Cognitive Speed Decline Early in DM

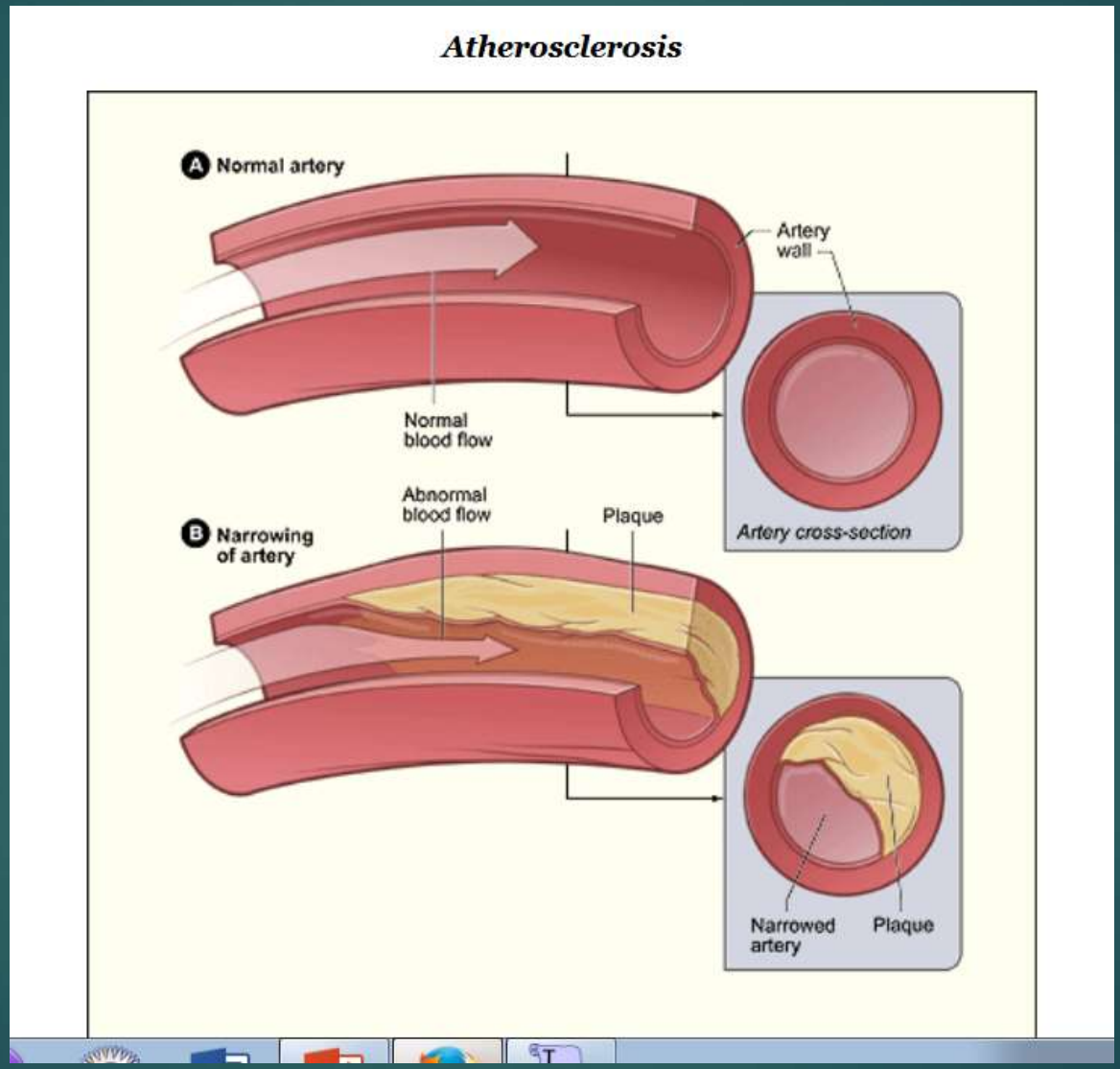
- 41 adults with diabetes and 424 adults in good health, between ages 53 and 90.
- Healthy adults perform significantly better than adults with diabetes on two of the five domains tested: executive functioning and processing speed
- There were no significant differences on tests of episodic and semantic memory, verbal fluency, reaction time and perceptual speed.
- Diabetes-linked cognitive deficits appear early and remain stable

Sophie E. Yeung , NP, 2009

Cardiovascular Risk Factors and Cognitive Functioning

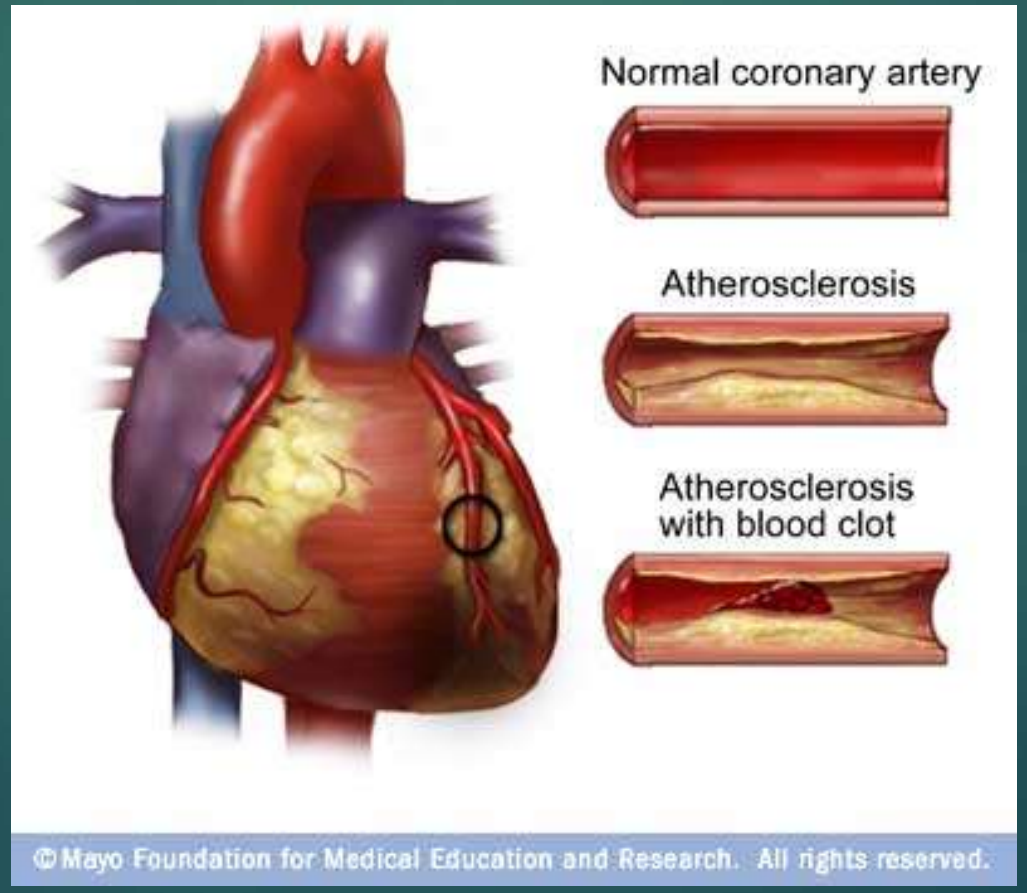
- There is cumulative impact of CVD risk factors on cognitive functioning
- For each risk factor at NP testing (WMS, COWAT, Similarities, Digit Span), risk of lower NP performance increased by 23% (Framingham study):
  - HTN
  - DM
  - Cholesterol
  - Smoking
  - Alcohol
  - Obesity
- DM > HTN > obesity > smoking = most effect
- Cumulative effect: More risks, more deficits

Atherosclerosis

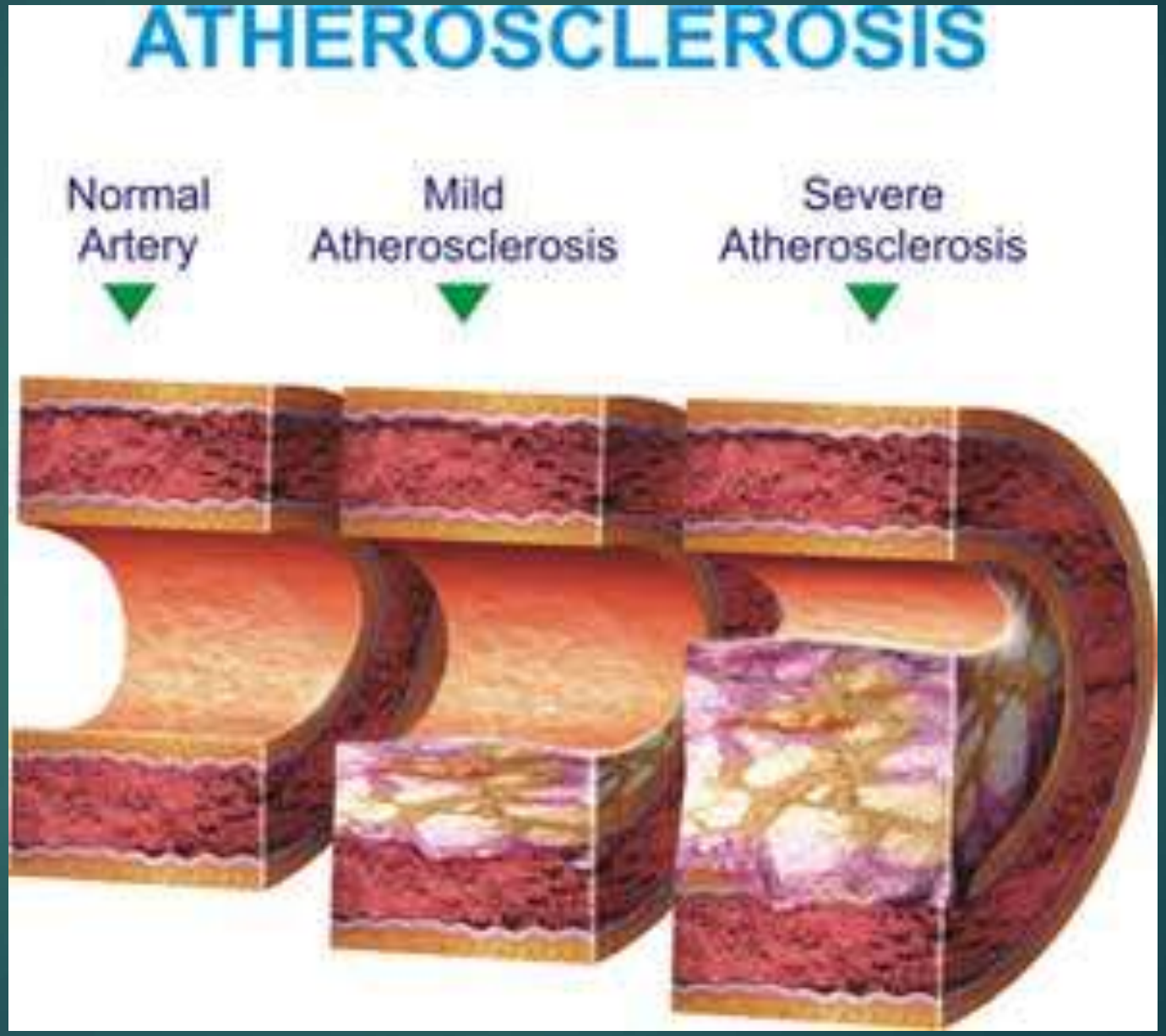


Atherosclerosis 1

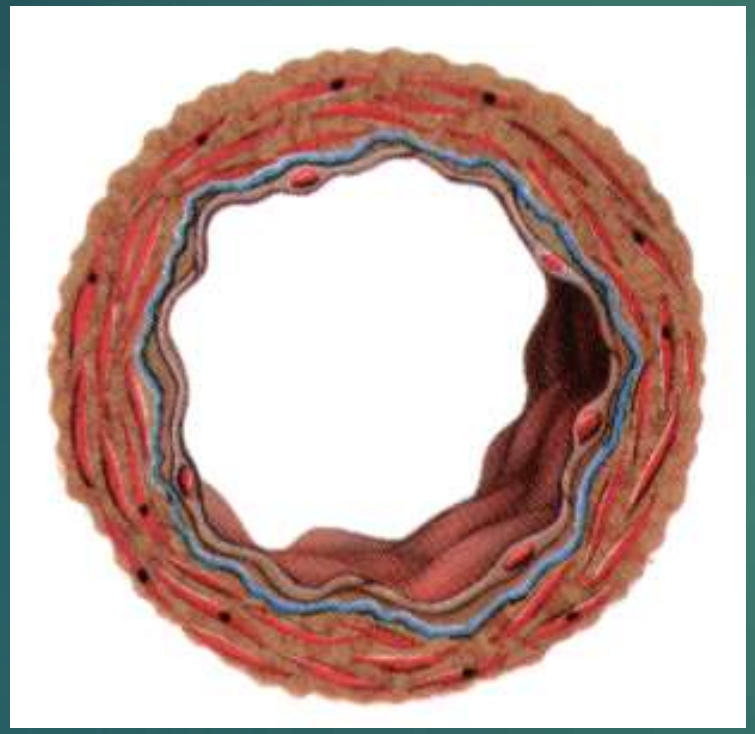
Atherosclerosis: disease of arteries in which lumen (interior space of tube) of the artery becomes narrowed by fatty deposits and fibrous tissue that accumulate in the intimal layer of vessel wall.

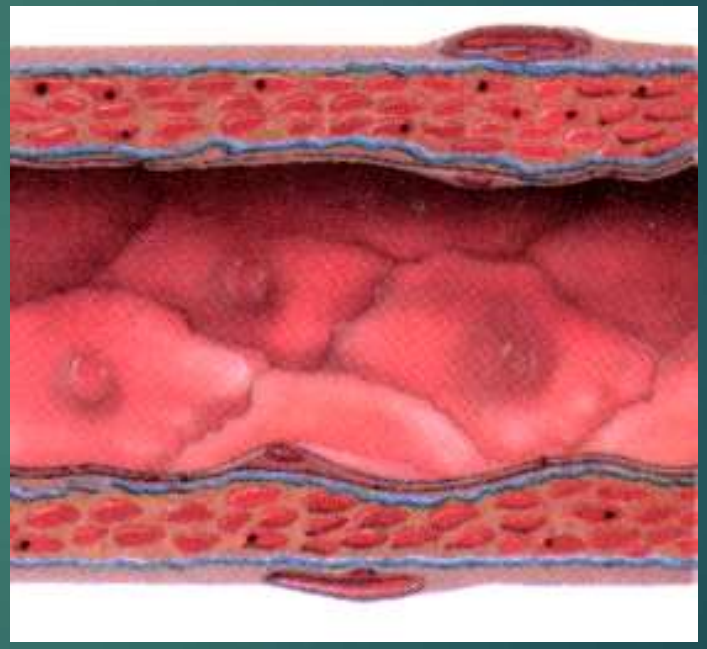


Atherosclerosis 2

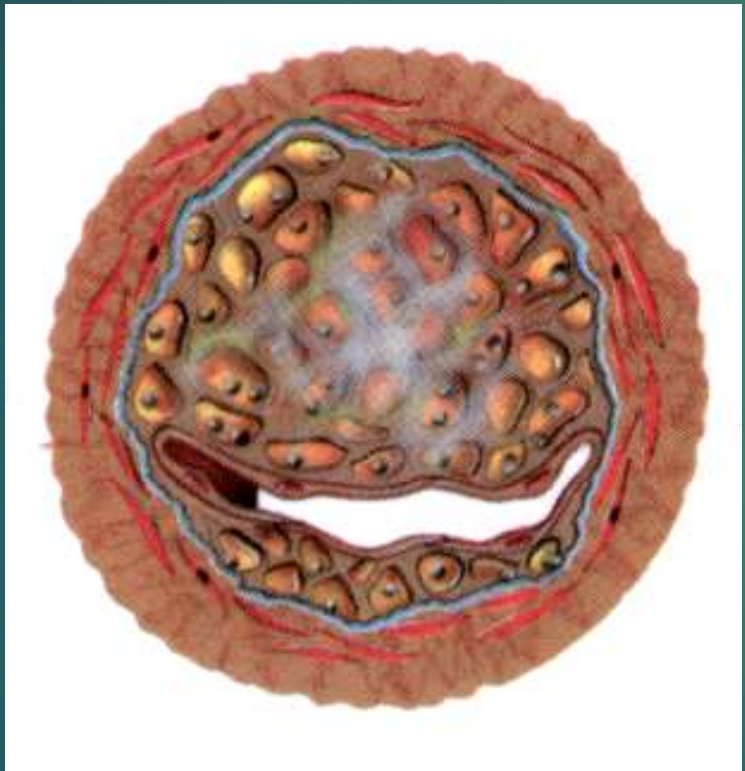


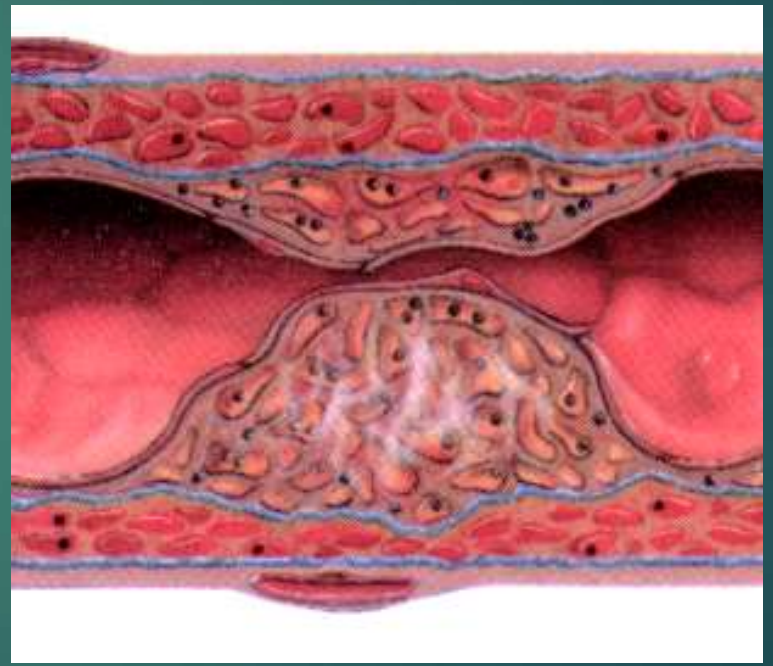
Normal Blood Vessel Wall





Plaque





Atherosclerosis and Cognitive Functioning

- Cause of Angina, MI, and stroke
- Risk factors: HTN, DM, Smoking, Hyperlipidemia
- In middle-elder aged, atherosclerosis related to decline in:
  - MMSE
  - TMT-B
  - Buschke Memory Test
  - Verbal Fluency
- Ultrasound of thickness of carotid arteries related to :
  - Digit Symbol
  - Delayed Recall

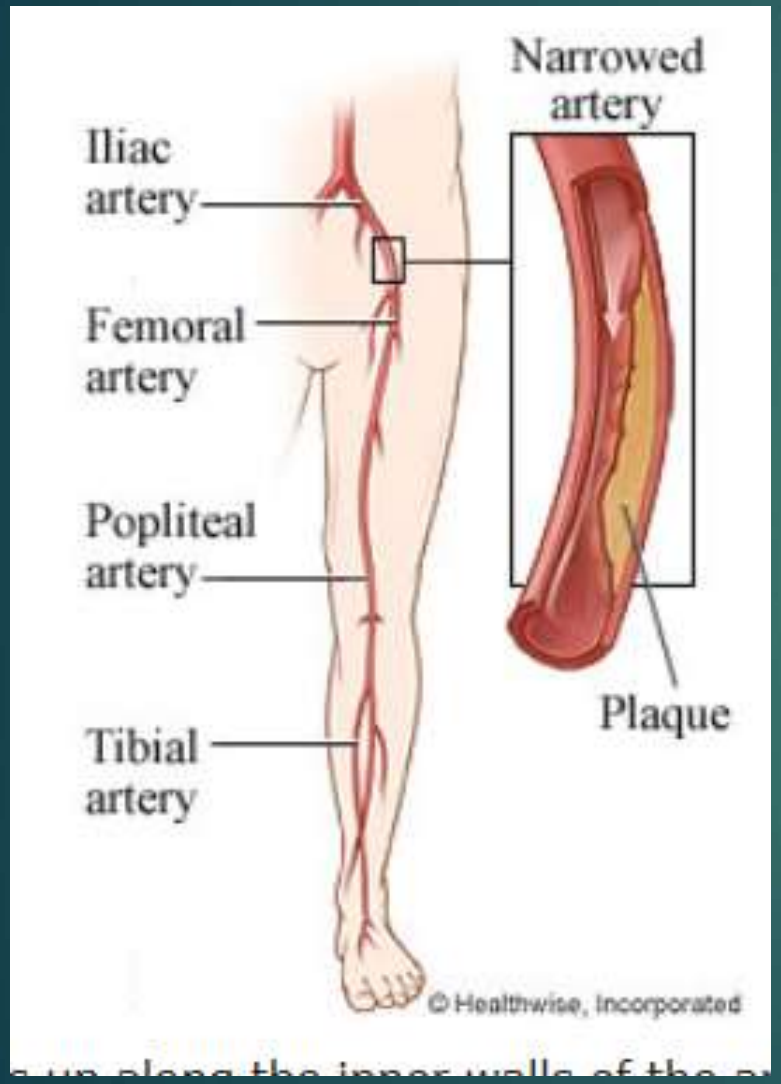
Dental Health & CV Health

- Tooth brushing less than twice a day is associated with cardiovascular disease, even after adjustment for age, sex, socioeconomic group, smoking, visits to dentist, BMI, family history of cardiovascular disease, hypertension, and diagnosis of diabetes.

- Gum disease increases risk of Alzheimer's

- Inflammation plays an important role in the pathogenesis of atherosclerosis, and markers of low grade inflammation have been consistently associated with a higher risk of cardiovascular disease

Peripheral Arterial Disease: PAD



- When PVD affects only the arteries and not the veins, it is called peripheral arterial disease (PAD).

- The main forms that PVD may take include:
  - blood clots (for example, deep vein thrombosis (obstructive clot) or DVT),
  - swelling (inflammation),
  - narrowing and blockage of the blood vessels.

Peripheral Vascular Disease (PVD/PAD)

- Chronic atherosclerotic occlusive disease of lower extremity arteries: leg pain on walking and weakness, amputation
- 50% die of MI (heart attack)
- 90% smokers (smokers make 20% more errors on MMSE)
- 10 % of pts with PVD s/p lower extremity amputation had significant cognitive deficits, esp. executive functioning
- Severity of PVD is an independent predictor of cognitive dysfunction

- Ischemic manifestations in heart and brain

PVD and NP effects

- Severity of PVD is an independent predictor of cognitive dysfunction
- Digit Symbol, WCST, TMT-B, Block Design, Rey Complex: 30-50% of PVD patients score below 5%tile
- Related to functional level 1 year later

Erectile Dysfunction: predictor of Cognitive and CV health

- Vascular disease is the most common etiology of erectile dysfunction (ED).
- Men with ED are at a 65% increased relative risk of developing coronary heart disease and a 43% increased risk of stroke within 10 years.
- Vietnam Era Twin Study of Aging: ED was associated with poorer cognitive performance, particularly on attention-executive-psychomotor speed tasks.

Moore, CS, et al. 2014

Cardiac Arrest

- 75% due to ventricular tachycardia (fast arrhythmia → ventricular fibrillation)
- Ischemic anoxia
- Only 15 of 100 survive out of hospital; Majority have neurological deficits due to anoxic damage
- Memory and frontal deficits
- Anterograde amnesia, decreased free recall, less decreased recognition
- Depression common

Cognitive Consequences of Cardiac Arrest

- Cardiac arrest:
  - Rats with ischemic hippocampal damage induced by bilateral carotid and vertebral occlusion showed deficits observed in cardiac arrest survivors – extensive damage to CA-1 region of hippocampus and permanent memory deficit

Cognitive Consequences of Myocardial Infarction, Arrhythmias, and Cardiac Arrest

- 1 million MI's/Heart Attacks in US annually, 500K fatal
- Caused by atherosclerosis
- Mechanisms: hypoxia, CV insufficiency, Strokes (3-5% after MI), depression (30%)
- Arrhythmias: 5x greater risk of stroke and hypoperfusion

Neurological Complications Of Heart Surgery

- Possible nervous system complications of bypass surgeries, aortic surgery, cardiac catheterizations, valve replacements, heart transplants and surgeries for congenital heart disease and heart tumors.
- In 2006, 1.3 million angioplasties and 448,000 bypass surgeries were performed in the United States
- Complications from bypass surgery include vision problems, paralysis, hoarseness, movement disorders and disturbances in learning, memory, attention, concentration and mental agility.
- Risk of stroke ranges from just under 1 percent to as high as 5 percent
- Complications of aortic surgery include stroke, paraplegia and peripheral nerve dysfunction

Love, Hocker, Bille, 2009

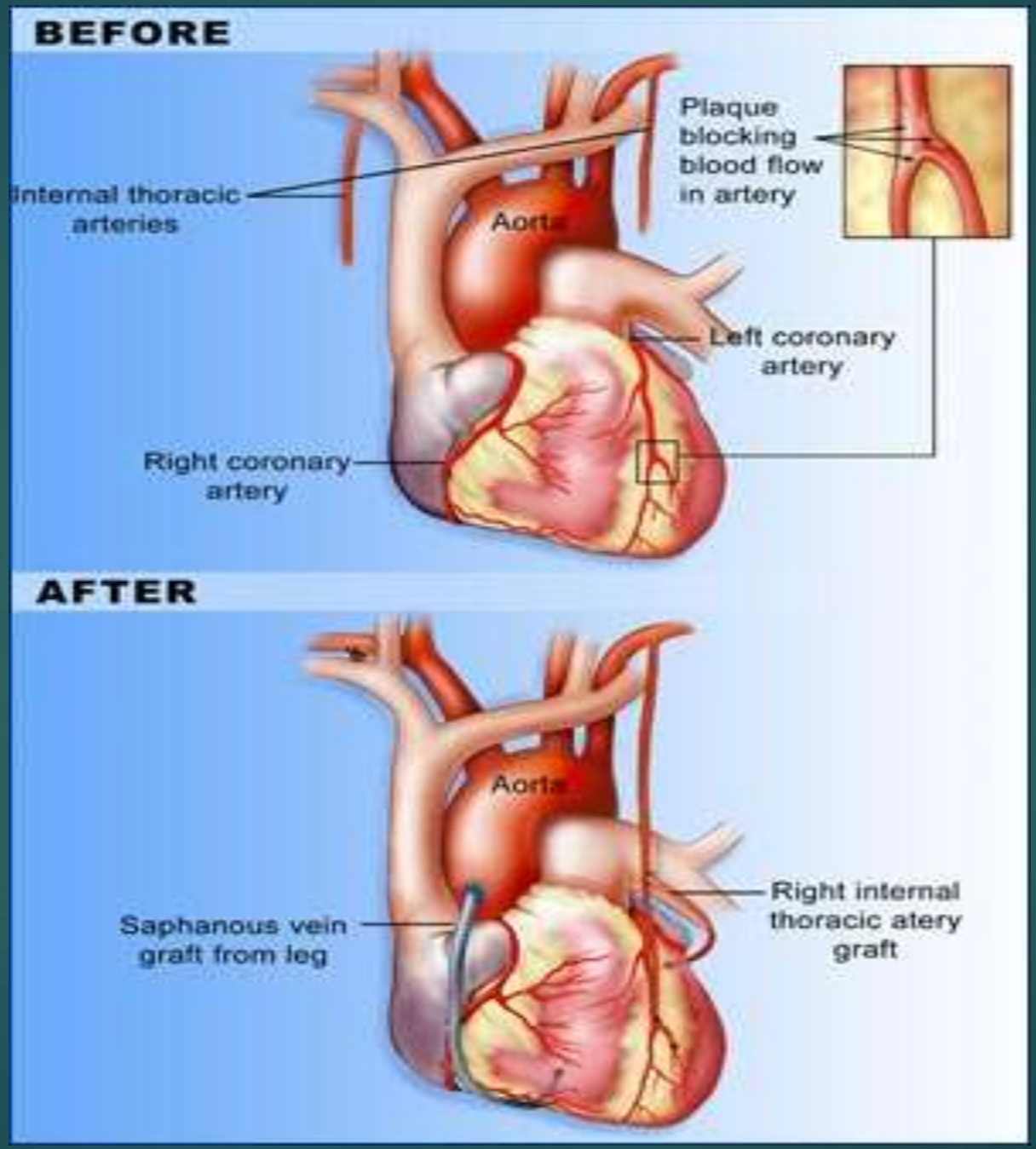
CABG

- Coronary artery bypass graft (CABG) is a surgery in which the arteries of the heart that are occluded or partially blocked by atherosclerosis (thickening of the heart due to plaque) and/or arteriosclerosis (hardening of the vessel) are bypassed with veins harvested from the patient's body.

- By bypassing these arteries, blood can again easily circulate throughout the body.

- Factors such as chronic hypertension, hyperlipidemia, etc. impact the health of the arteries.

CABG


BEFORE
Internal thoracic arteries
Aorta
Plaque blocking blood flow in artery
Left coronary artery
Right coronary artery
AFTER
Aorta
Saphanous vein graft from leg
Right internal thoracic atery graft

CABG 2

- The saphenous vein specifically is usually harvested, as it is a large vein in the leg that can often be retrieved through endoscopy.

- A cardiopulmonary bypass (CPB) machine is used so that the surgeon can operate on a still heart and in a bloodless field. The bypass machine is connected to the aorta and a solution is administered to cause cardioplegia (arrest of the heart).

- The body temperature is also cooled to about 36 degrees, but it can drop lower

Post-operative cognitive deficits: emboli cause theory

- During this on-pump time (the length of time the CPB machine is connected), the only circulation of blood throughout the body is that from the CPB. The clamping of the aorta can loosen thrombi (accumulation of plaque), causing emboli to be released into the bloodstream.

- These emboli can cause ischemic stroke in the brain, and the removal of the aortic clamp also can create more emboli.

Neuropsychological Consequences of Coronary Artery Bypass Surgery (CABG)

- Increase in post surgical strokes (1.5-5.2%); neurological cause of death (18%)
- Old theory: Lowered perfusion and microemboli (gas or particulates)
- Risk factors: age, being female, APO-E 4
- Neuropsych. Deficits in 0-70%:
  - Memory, Attention
  - VS, Language

CABG 2

- Short term NP deterioration from preoperative status within 7-14 days after CABG; 13 to 79% have deficits 1 week post; 7 to 57% at 6 months
- Newman: 5 year longitudinal study of 261 pts
  - 53% significant cognitive decline at discharge
  - 42% at 5 years
  - “Just not the same” after surgery
- 10% of noncardiac surgery show post-op cognitive dysfunctions for up to 2 years

Is CABG or CAD the Culprit

- CV disease itself, and not any particular treatment, is the cause for cognitive decline in CABG

- 2008 study: 152 heart disease patients who were scheduled to undergo bypass surgery and 92 patients whose doctors planned to treat their heart disease in other ways, including stents and medications; 3 months, 1 year, 3 years, and 6 years after treatment cognitive assessments

- Over the next five years, most of the patients experienced a similar decline of cognitive function in almost every area tested, regardless of whether they had surgery or another treatment.

- Coronary artery disease is the culprit.

CABG: pre-surgical NP status

- Evidence that a considerable proportion of candidates for CABG have impaired cognitive performance even before surgery.
-
- The frequency of preoperative cognitive impairment has been reported to range from 20 to 46%,
- Preoperative MRI studies have also documented a high prevalence of small-vessel ischemic disease, lacunar infarctions, and other brain abnormalities
- Patients with such preexisting imaging abnormalities or cognitive impairment have been shown to have worse postoperative cognitive outcomes than patients with normal preoperative findings.

Latest, but small study

- On-pump CABG patients (n = 16), thoracic surgical patients (n = 15), and a nonsurgical control group (n = 15)
- CABG patients performed worse on every subtest before the operation, and this disadvantage persisted after the operation. Anxiety, depression, and stress were associated with impaired cognitive performance in the surgical groups 1 week after the operation: 44% of CABG patients and 33% of surgical control patients were significantly impaired; yet, by 8 weeks, nearly all patients had recovered to preoperative levels, with 25% of CABG and 13% of surgical control patients improving beyond their preoperative performance.
- Conclusions: Stress, anxiety, and depression impair cognitive performance in association with CABG and thoracic operations. Most patients recover to, or exceed, preoperative levels of cognition within 8 weeks. Thus, after controlling for nonsurgical factors, the prospects of a tangible improvement in cognition after CABG are high.

CABG cognitive outcomes

- Early studies reported a high prevalence of cognitive impairment after CABG, possibly attributable to surgical factors, such as anesthesia and cardiopulmonary bypass.
- Later studies suggested that much cognitive impairment after CABG predated the procedure and was related to patient factors, such as age, education, and vascular disease.
- Studies of carotid revascularization have reported mixed cognitive outcomes, with some suggesting early improvement.
- Studies of cardiac valve procedures and catheter ablation for atrial fibrillation commonly report imaging-detected cerebral emboli, but cognitive outcomes have been less clear.

2015 Review: Little adverse cognitive effect to CABG

- CABG may have little persistent adverse cognitive effect in older adults, and cognitive outcomes seem similar among the CABG approaches and between surgical and endovascular carotid revascularization. But mostly low to insufficient SOE (strength of evidence).
- Results suggest that persistent cognitive impairment after the studied cardiovascular procedures may be uncommon or reflect cognitive impairment that was present before the procedure.
- For CABG versus medical management, 1 eligible cohort study with substantial methodological limitations suggested that CABG may be associated with a transient cognitive benefit in older adults and little to no intermediate- to long-term cognitive impairment. Results also showed no differences in intermediate- or long-term cognitive outcomes between on- versus off-pump CABG treatment groups.
- Results from 1 study suggesting that transapical TAVR was associated with greater risk for cognitive decline than SAVR were prone to several important sources of bias and were essentially uninterpretable. No eligible studies reported data on cognitive outcomes after percutaneous coronary intervention or catheter ablation of atrial fibrillation in older adults.
- Need for NP assessment pre and post.

Howard A. Fink, et al., Ann Int Med, 2015

Post-operative cognitive deficits: POCD

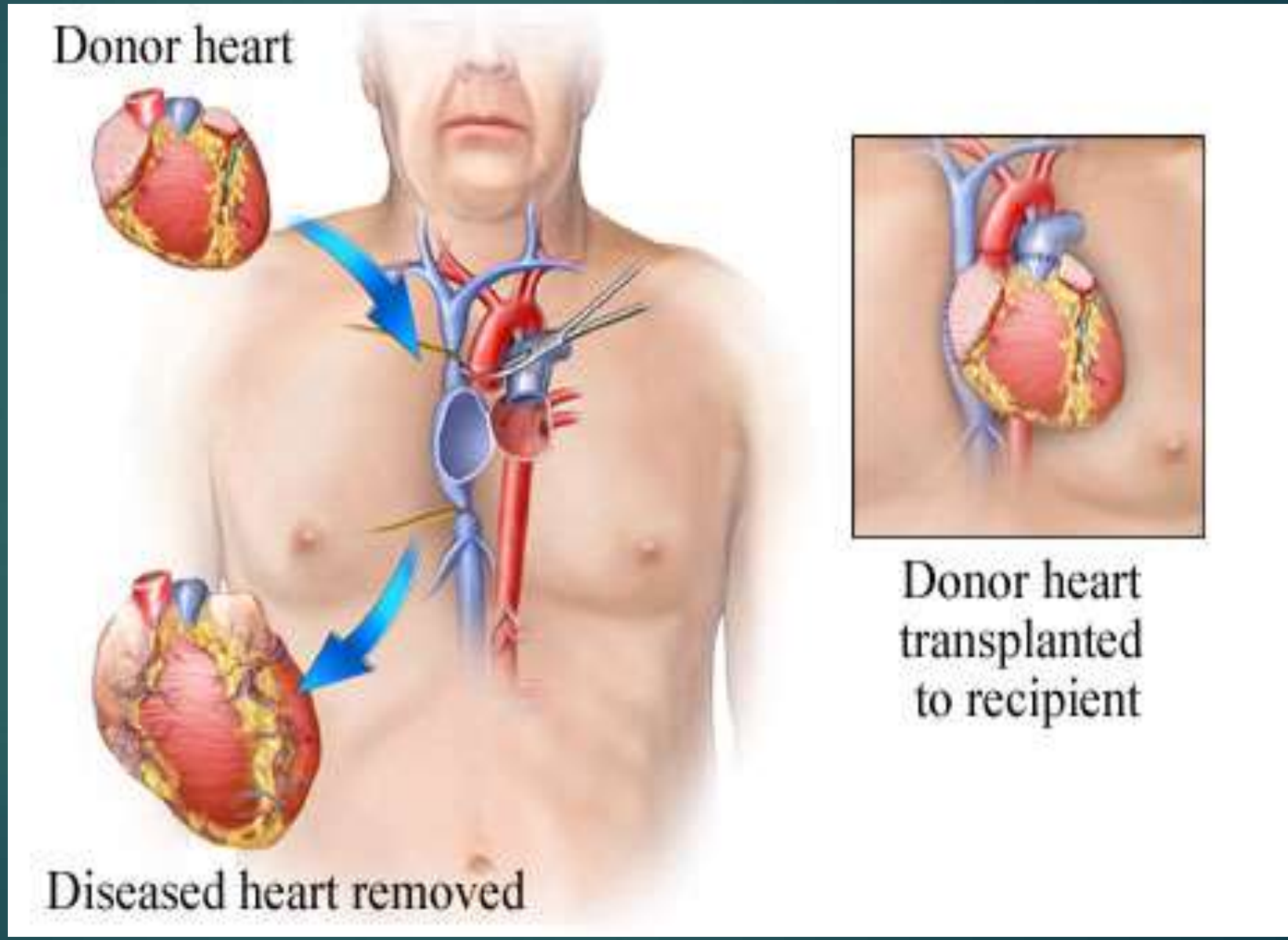
- While post-operative cognitive deficits (POCD) can occur with anesthesia in general, they are usually most pronounced after CABG.
- In addition to the effects of the anesthesia, you have the potential emboli, the diffuse inflammatory response of the body, and hypoperfusion of blood to the brain that all contribute to POCD in CABG.
- Delirium after CABG is common, while persistent cognitive deficits are variable.
- Some studies have reported cognitive deficits 3-years post-op. Increased age, intraoperative hyperglycemia, cerebral oxygen desaturation, and pre-op levels of depression and anxiety have all been attributed to impacting the extent and nature of POCD.
- Unassessed AD pathology too!

POCD:

- Postoperative cognitive dysfunction (POCD) is a decline in cognitive function that occurs after surgery. POCD after noncardiac surgery has been associated with increased mortality, decreased quality of life, risk of early withdrawal from the workforce, and increased dependency.
- The first International Study of POCD reported the incidence of POCD in patients 60 years or older to be 25.8% and 9.9% 1 week and 3 months after major noncardiac surgery, respectively.
- A total of 69 patients aged 65 years or older undergoing major noncardiac surgery were enrolled. Patients' cognitive function was assessed before and 3 months after surgery using a computerized neurocognitive battery. A nonsurgical control group of 54 older adults was recruited to adjust for learning effects from repeated administration of neurocognitive tests
- POCD was observed in 15.9% of older adults after major noncardiac surgery. Risk factors for POCD in these patients were carrying the APOE4 genotype, using one or more highly anticholinergic or sedative-hypnotic drugs prior to surgery, and receiving sevoflurane for anesthesia.

O. A. Shoair, M. P. Grasso II, [...], & P. W. Slattum, J Anaesthesiol Clin Pharmacol. 2015 Jan-Mar; 31(1): 30–36.

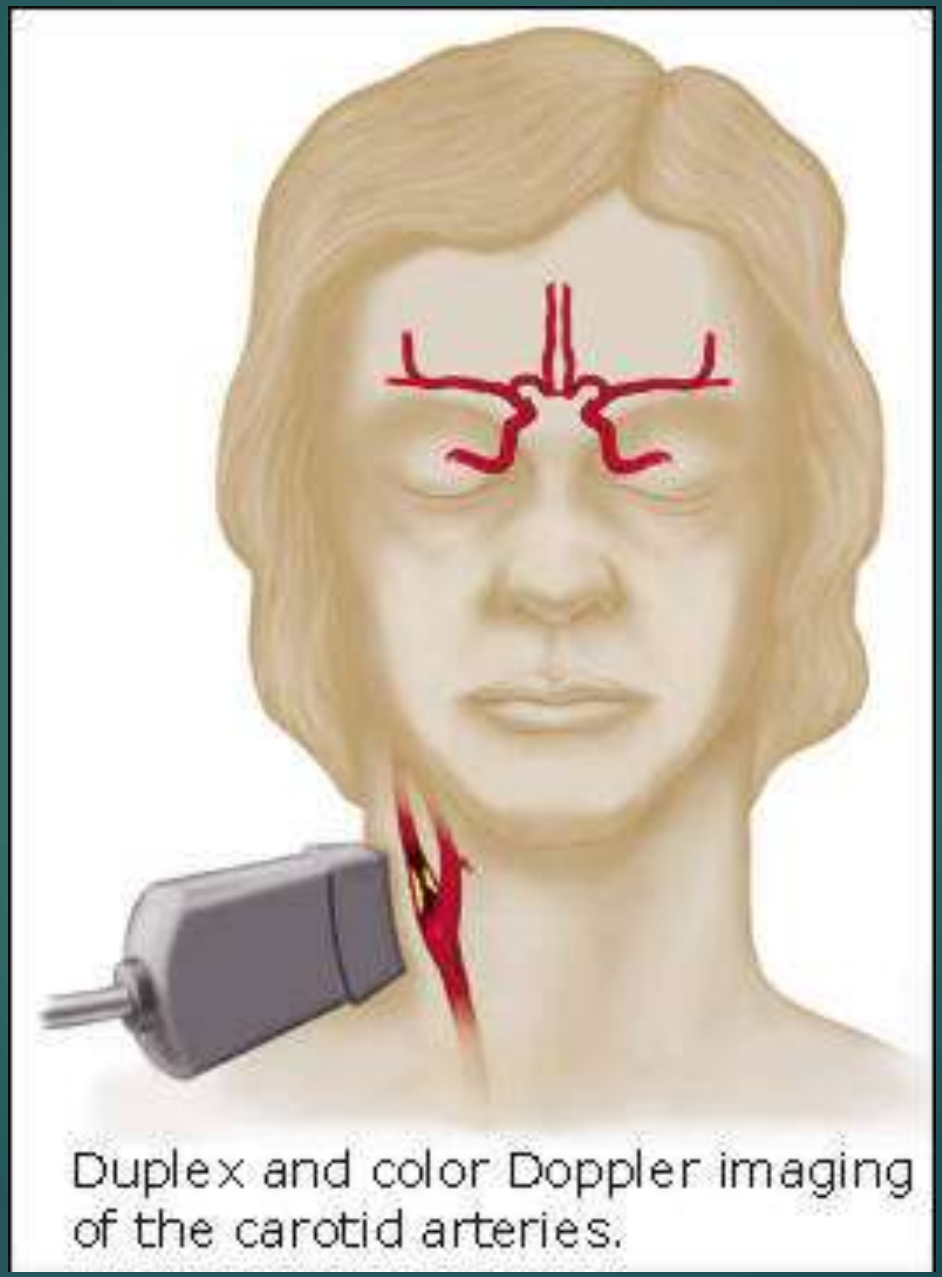
Heart Transplant



Neuropsychology of Heart Transplantation

- 2300 Heart Transplants in US each year: 77% male, 82% Caucasian, 45% have 10 y survival
- Cardiomyopathy is most common dx
- Presurgical deficits: memory, motor speed, abstraction ↓; depression (30%)
- Mechanisms: reduced oxygenation (brain uses 20% of all body oxygenation; 15% cardiac output; significant relation to right arterial pressure)
- Postsurgical: few studies, noting NP improvement; memory ↓

Evaluation of carotid arteries

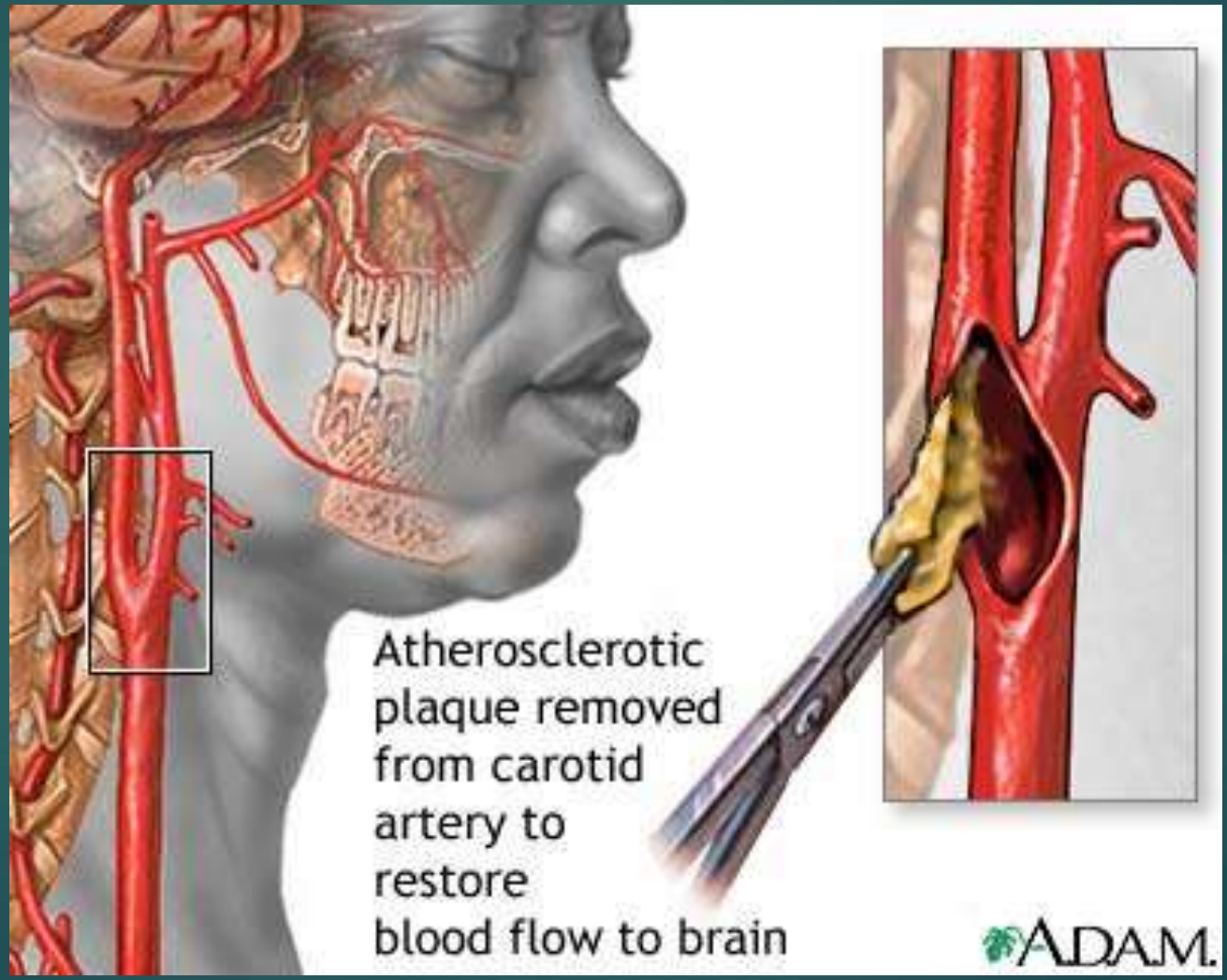


Duplex and color Doppler imaging of the carotid arteries.

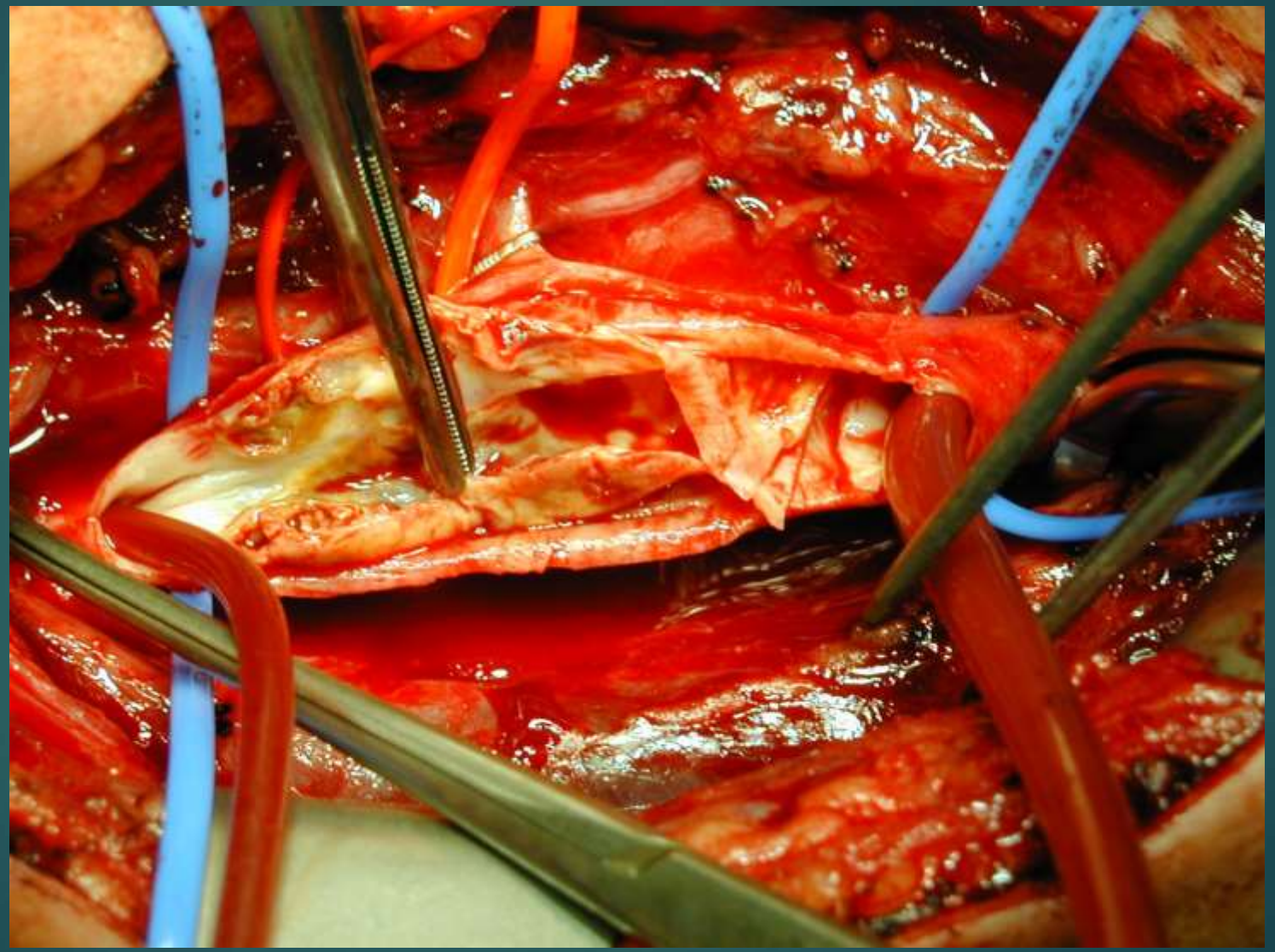
Carotid Stenosis and Carotid Endarterectomies

- Clogged internal carotids can result in syncopal episodes, greatly increased risk of stroke, and cognitive decline due to microembolisation in the cerebral arteries
- Endarterectomy can reduce the long-term risk of Stroke
- There is a risk of intra- or post-operative Stroke due to particulate microembolisation (2 – 7%).
- Microembolisation also a recognized cause of decreased cognitive function in pts with mechanical heart valves and suggested etiology in pts with atrial fibrillation

Carotid Endarterectomy



Carotid Endartectomy



Carotid Endarterectomy

- Carotid artery supplies anterior 2/3 of brain
- Reduces & increases risk of stroke in focal neurological sxs (aphasia, motor numbness) and in narrowing of 70-99%: 16.5% reduction
- Theories:
  - Microembolic showers as cause of NP deficits & TIAs before and after CE
  - CBF ↓
  - Appears to improve cognition.

Increased Microbleeds with Age

- Cerebral microbleeds are highly prevalent in the aging brain – and not primarily products of stroke-related injury, hypertension or AD.
- Cerebral microbleeds were identified in 22 of 33 cases – all occurring in capillaries, the small blood vessels of the brain.
- Found a substantially higher rate of incidence than that reported in MRI studies, which have shown microbleeds in 18 percent of people between 60 and 69 and in 38 percent of those over 80.
- Drugs that interfere with platelets and blood clotting, such as aspirin, are known to be associated with microbleeds
- **Conclusions and Relevance** In the general population, a high microbleed count was associated with an increased risk for cognitive deterioration and dementia. Microbleeds thus mark the presence of diffuse vascular and neurodegenerative brain damage.

Microbleeds

- Cerebral microbleeds are hypothesized downstream markers of brain damage caused by vascular and amyloid pathologic mechanisms
- Study: 3257 participants (1758 women, 59.6 [7.8] years) underwent baseline and follow-up cognitive testing. Microbleed prevalence was 15.3%. The presence of more than 4 microbleeds was associated with cognitive decline. Lobar (with or without cerebellar) microbleeds were associated with a decline in executive functions, information processing, and memory function, whereas microbleeds in other brain regions were associated with a decline in information processing and motor speed. After a mean (SD) follow-up of 4.8 (1.4) years, 72 participants developed dementia, of whom 53 had Alzheimer dementia. The presence of microbleeds was associated with an increased risk for dementia, including Alzheimer dementia.
- **Conclusions and Relevance** In the general population, a high microbleed count was associated with an increased risk for cognitive deterioration and dementia. Microbleeds thus mark the presence of diffuse vascular and neurodegenerative brain damage.

Stroke

History of Stroke

- 1658: Johanne Wepfer discovers that stroke can be caused by occlusion of cerebral vessels or by hemorrhage

- Used to be called *apoplexy* or an *apoplectic attack*, now called a *stroke*.

Famous Persons with Strokes

- Vladimir Lenin, age 52
- Woodrow Wilson
- Franklin D. Roosevelt
- Winston Churchill
- Joseph Stalin

Stroke

- Stroke is the most common type of cerebrovascular disease
- The archaic term “cerebrovascular accident “ should not be used.
- Fifth most common neurological disorder in the US.
- Leading cause of functional disability

Prevalence

- 800,000 new strokes in US every year; 200, 000 recurrent; 5.5 million survivors; 13 million with silent strokes
  - On average, one stroke every 45 seconds
- 3rd leading cause of death in USA
- Age is greatest risk factor.
- Women 3x greater risk in 45 to 54 age

Stroke

- Rapid onset of nonconvulsive neurological deficits
- Any CNS disturbance related to alteration of cerebral blood flow (CBF)
  - Ischemic (infarction, arterial blockage)= 87%
    - Obstruction of blood flow by thrombosis or embolism
  - Hemorrhagic (bleeding into brain) = 13%

Stroke

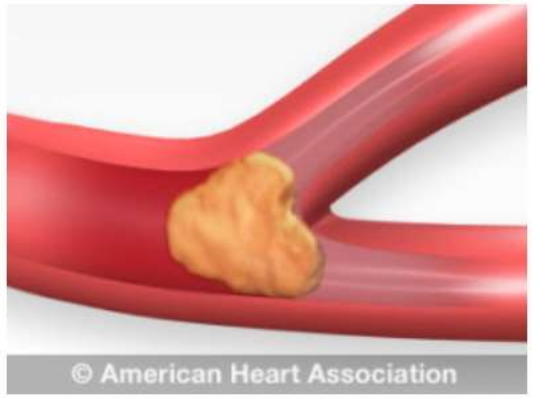
- Acute episodic neurological deficit
  - TIA-focal neurological deficit that resolves in 24 hrs
  - RIND (Reversible ischemic neurological deficits) >24 h<7 days

- Cerebral Infarction 80%
  - Atherosclerotic 60%
  - Cardiac emboli 15%
  - Other 5%
- Intracranial hemorrhage 15%
- Nondramatic SAH 5%
- Venous Occlusion 1%

A blockage and resulting area of damage

Ischemia, Hemorrhage, TIA

Ischemic (Clots)



Ischemic stroke occurs as a result of an obstruction within a blood vessel supplying blood to the brain. It accounts for 87 percent of all stroke cases.

Hemorrhagic (Bleeds)

Hemorrhagic stroke occurs when a weakened blood vessel ruptures. Two types of weakened blood vessels usually cause hemorrhagic stroke: aneurysms and arteriovenous malformations (AVMs). But the most common cause of hemorrhagic stroke is uncontrolled hypertension (high blood pressure).

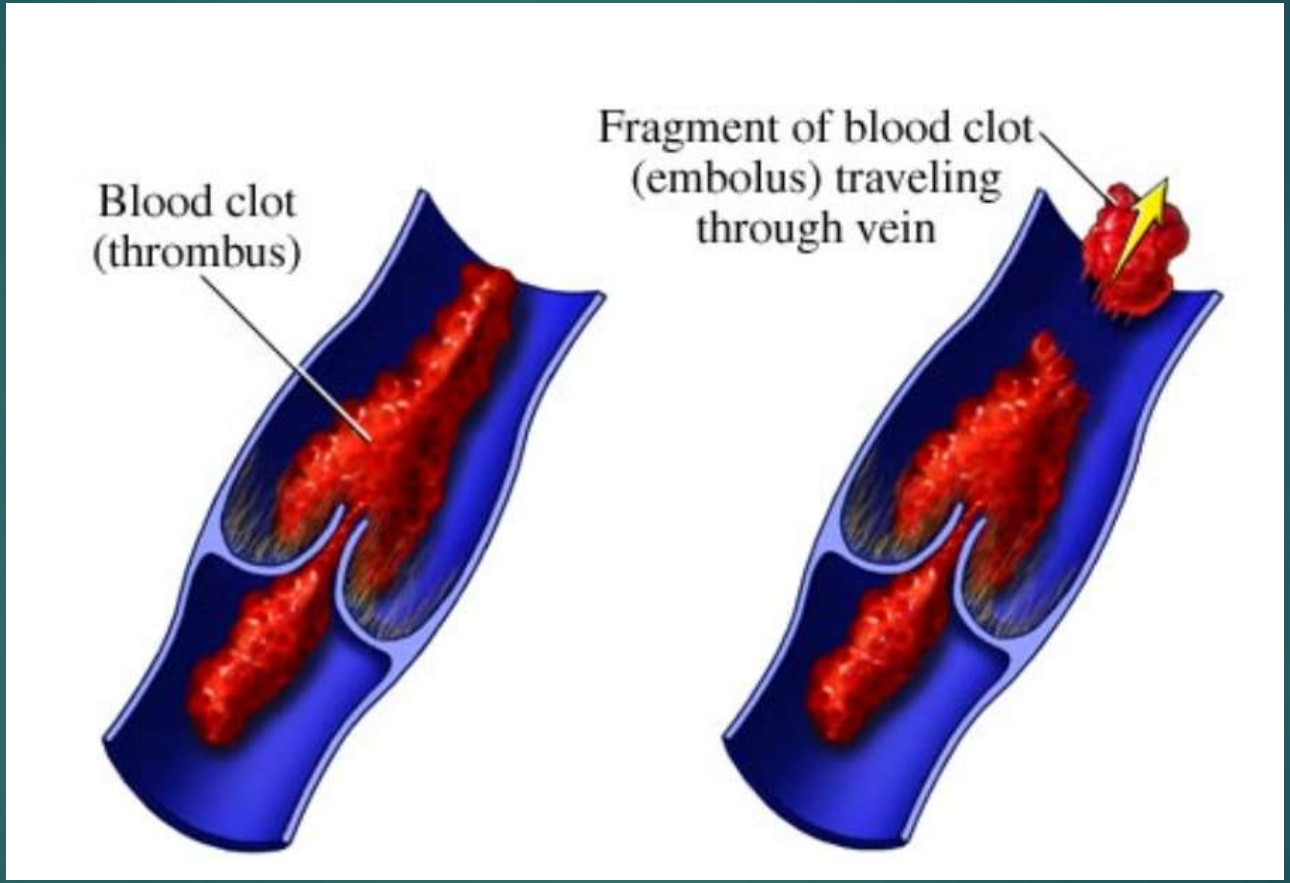
TIA (Transient Ischemic Attack)

TIA (transient ischemic attack) is caused by a temporary clot. Often called a "mini stroke", these warning strokes should be taken very seriously.

Block	Bleed	Transient
Ischemia	Hemorrhage	TIA

Illustration of occlusions

A **thrombus** is a solid mass of platelets and/or fibrin (and other components of blood)



An **embolus** is most often a piece of a thrombus that has broken free and is carried toward the brain by the bloodstream

Stroke

- Mortality: 25% in 1st month, 50% in 5 years
- Survivors:
  - 48% hemiparesis
  - 22% non-ambulatory
  - 25-50% ADL difficulty or dependence
  - 32% depression
- Stroke effect: depends on area, necrosis, edema
- Hypertension: major risk factor

Stroke Mechanisms

1- Large vessel:

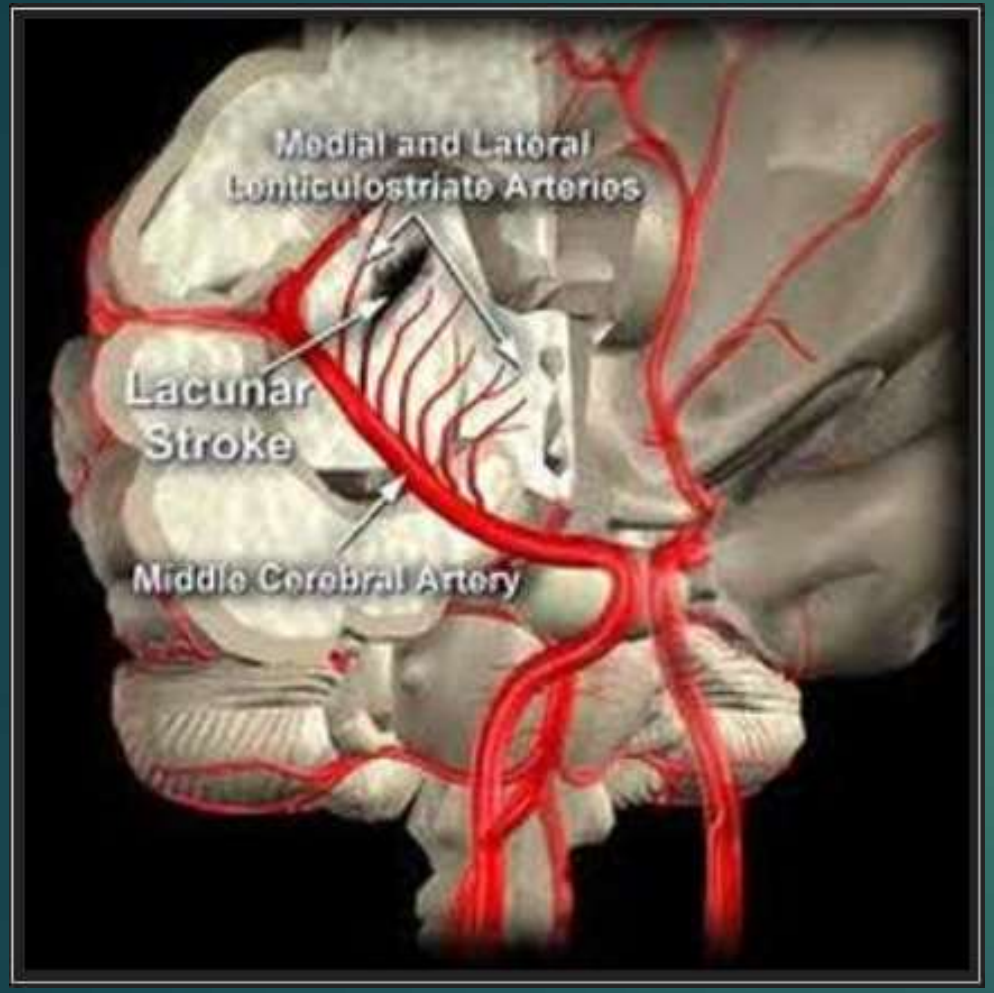
- Atherosclerosis is most common pathology, a plaque thrombus (formation or presence of a blood clot in a blood vessel).
- Enlargement of plaque
  - → narrow/occlusion of vessel
  - → stenosis

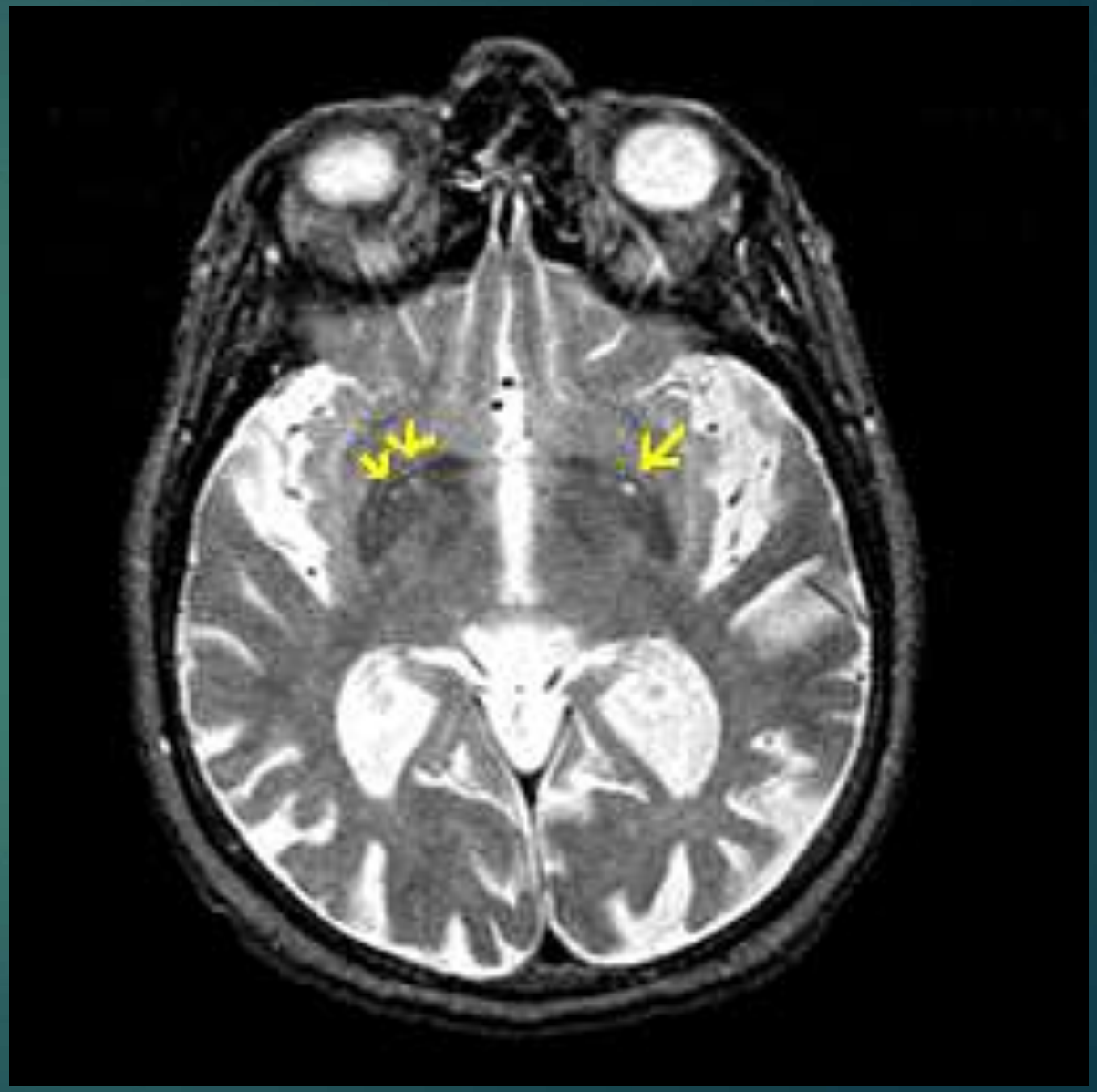
Stroke Mechanisms 2

2 - Small Vessel:

- Narrowing, weakening, leakage, aneurysm: most common in Caudate, Putamen, Thalamus, Internal Capsule, Pons, Cerebellum
- Lacunar – deep infarcts due to small artery occlusions & appear on MRI as <1.5 cm areas; Account for 15-20% of strokes; inverse relationships with executive functioning
- 4 lacunar syndromes:
  - Pure motor hemiparesis (IC, Pons)
  - Pure sensory strokes (Thalamus)
  - Dysarthria (clumsy hand syndrome) (IC, Pons)
  - Ataxic hemiparesis (Pons, IC)

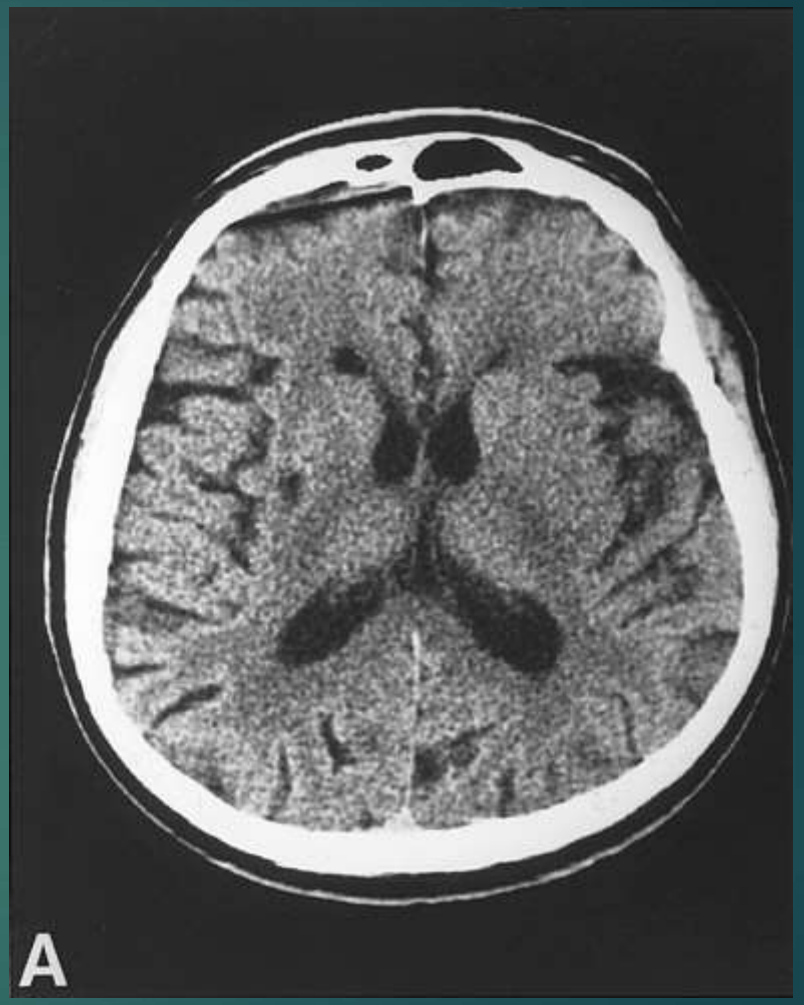
Lacunar infarcts





Lacunes

- Small subcortical infarcts from occlusion of a penetrating artery.
- Account for 15-20% of strokes
- Common in patients with HTN which leads to eventual thrombosis



Lacunes and Executive Functioning

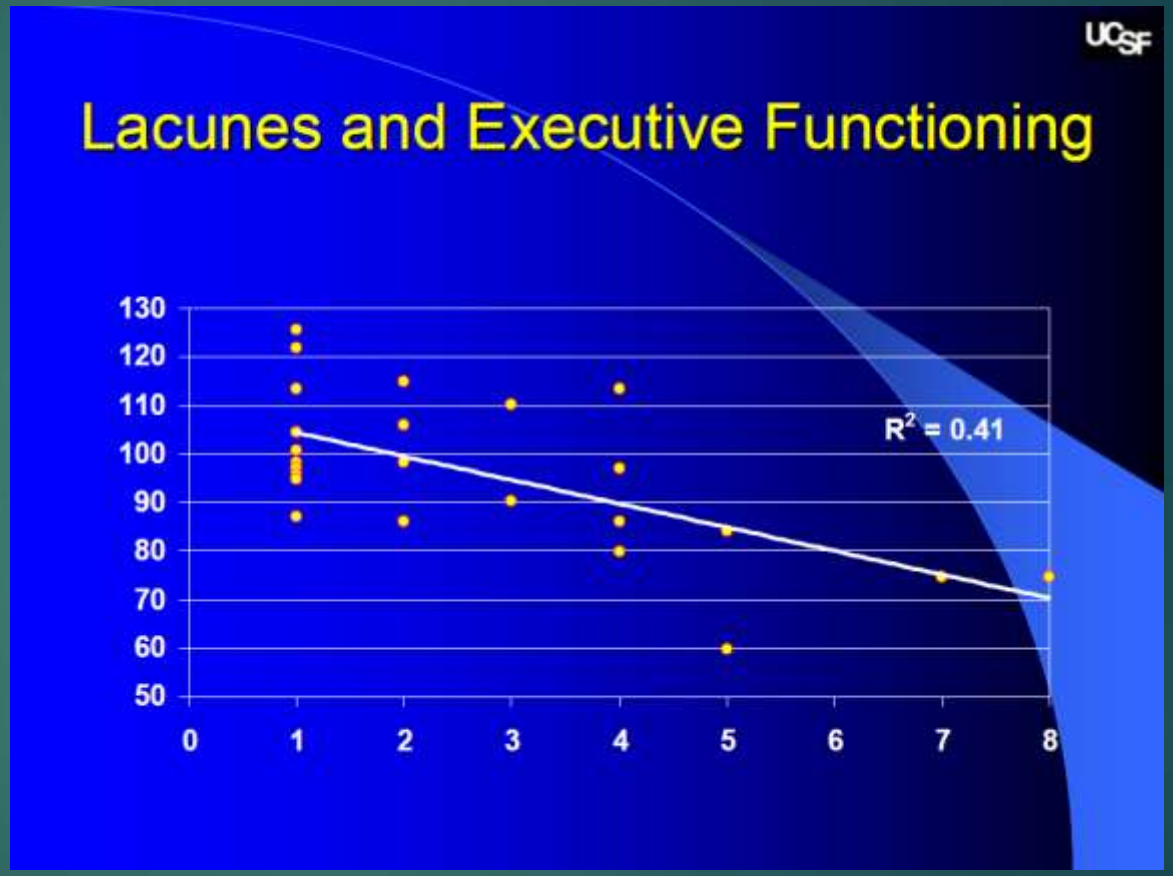
- In normal subjects, the number of
  - subcortical lacunes
  - and volume of WM subdural hematomas
- have inverse relationships with executive functioning.

Common Lacunar Syndromes

TABLE 10.3 Common Lacunar Syndromes

SYNDROME	CLINICAL FEATURES	POSSIBLE LOCATIONS FOR INFARCT	POSSIBLE VESSELS INVOLVED
Pure motor hemiparesis or dysarthria hemiparesis	Unilateral face, arm, and leg upper motor neuron–type weakness, with dysarthria	Posterior limb of internal capsule (common)	Lenticulostriate arteries (common), anterior choroidal artery, or perforating branches of posterior cerebral artery
		Ventral pons (common)	Ventral penetrating branches of basilar artery
		Corona radiata	Small middle cerebral artery branches
		Cerebral peduncle	Small proximal posterior cerebral artery branches
Ataxic hemiparesis	Same as pure motor hemiparesis, but with ataxia on same side as weakness	Same as pure motor hemiparesis	Same as pure motor hemiparesis
Pure sensory stroke (thalamic lacune)	Sensory loss to all primary modalities in the contralateral face and body	Ventral posterior lateral nucleus of the thalamus (VPL)	Thalamoperforator branches of the posterior cerebral artery
Sensorimotor stroke (thalamocapsular lacune)	Combination of thalamic lacune and pure motor hemiparesis	Posterior limb of the internal capsule, and either thalamic VPL or thalamic somato-sensory radiation	Thalamoperforator branches of the posterior cerebral artery, or lenticulostriate arteries
Basal ganglia lacune	Usually asymptomatic, but may cause hemiballismus (see KCC 16.1)	Caudate, putamen, globus pallidus, or subthalamic nucleus	Lenticulostriate, anterior choroidal, or Heubner's arteries

Memory & executive function correlate negatively with brain infarcts, especially infarcts in cortical and sub-cortical gray matter.



Transient Ischemic Attacks (TIA)

- Temporary obstruction of a blood vessel; usually caused by a temporary clot
- A temporary focal neurological deficit due to retinal or focal brain ischemia with clinical sxs lasting less than 1-24 hours and in absence of acute infarction on MRI
- Associated with atherosclerotic disease
- Get to ER!

TIA: Transient Ischemic Attack

- 30 % of TIAs have stroke in 5 years
- Strong predictors of subsequent stroke: (9% of TIAs have stroke in 90 days; 4-8% in 1st month; 12% 1st year, 24-29% in 5 years)
- TIA reduces survival by 4% in the first year and by 20% within 9 years.
- TIA has a minimal effect on mortality in patients <50 years old but heralds significant reduction in life expectancy in those >65 years.

TIA

- 50% of all people who have a major stroke following a warning stroke (a transient ischemic attack or mild stroke) have it within 24 hours of the first event; get to ER!

- Strong predictors of subsequent stroke: (9% of TIAs have stroke in 90 days; 4-8% in 1st month; 12% 1st year, 24-29% in 5 years)

- Half of these early recurrent strokes being disabling or fatal

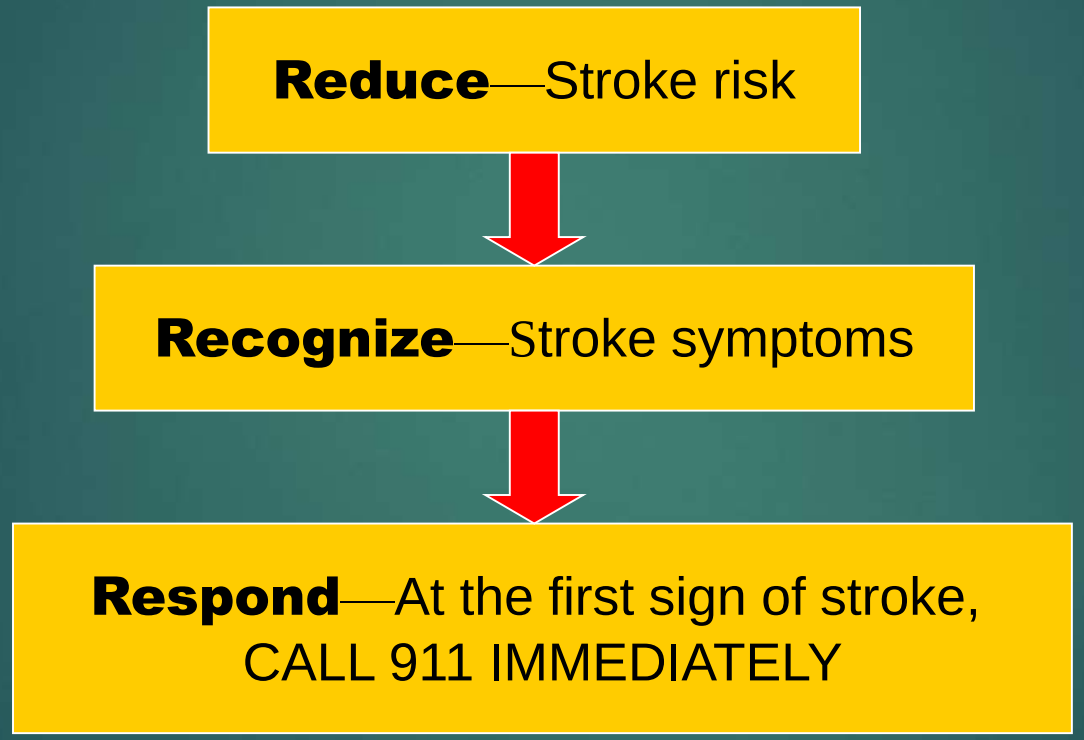
TIAs

- Of 1,247 first TIA or strokes, 35 had recurrent strokes within 24 hours, all in the same arterial area.

- 42% of all strokes during the 30 days after a first TIA occurring within the first 24 hours

Chandratheva A et al. Neurology. 2009: 72(22);1941-7

Be Stroke Smart



TIA & Executive Dysfunction

- 140 patients (average age 67) admitted to the Urgent TIA Clinic at the London Health Sciences Center in London, Ontario.
- Within a week of symptom onset: Executive functions were impaired in almost 40 percent of the TIA and minor stroke patients.
- "Transient ischemic attacks and minor strokes are not just a warning of future stroke. They are an indication that the process of brain injury may have begun.

- 50% of pts who had NP testing following TIA had NP deficits

- Do MRI and NP testing

Stroke: Symptoms

- Sudden numbness, weakness, or paralysis of your face, arm or leg -- usually on one side of the body
- Sudden difficulty speaking or understanding speech (aphasia)
- Sudden blurred, double or decreased vision
- Sudden dizziness, loss of balance or loss of coordination
- A sudden, severe "bolt out of the blue" headache or an unusual headache, which may be accompanied by a stiff neck, facial pain, pain between your eyes, vomiting or altered consciousness
- Sudden confusion or problems with memory, spatial orientation or perception

Hip Hop Signs of Brain Attack

- *There's a brand new dance that's sweepin' the nation by the National Stroke Association …*
- *… For those who can dance and clap your hands to it…*
- *One arm as you slur every word you speak.*
- *Imitate like you're paralyzed and weak…*
- *Walkin' funny … stagger unsteady.*
- *Stand in a line and pretend that you're BLIND…Loss of vision is one of the very first signs!*
- *A twisted face will show that you're ready.*
- *To do that dance that they call the STROKE!!*
- *Ice pick headache. IT AIN'T NO JOKE*
- Highest risk for stroke is among African Americans

5 Signs of Stroke

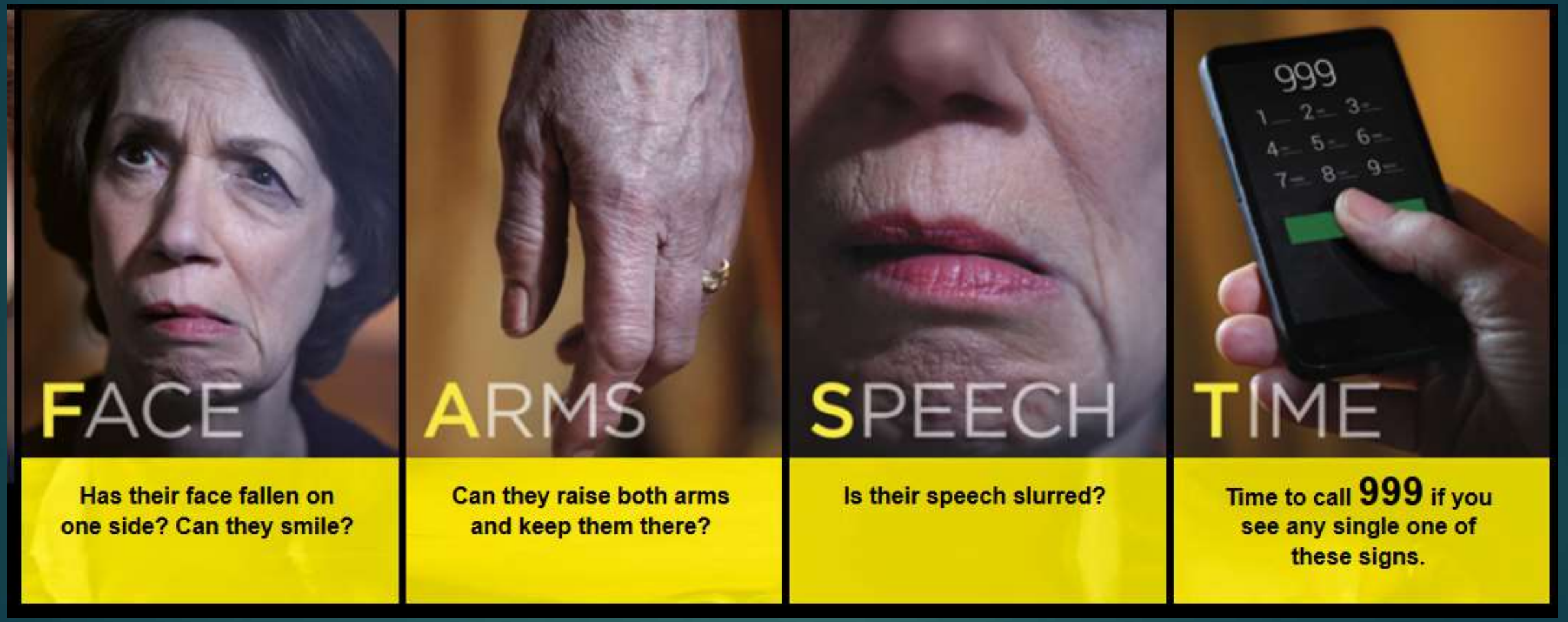
- Walk - Is balance off – 1 side off
- Talk – speech slurred, face droopy
- Reach – 1 side weak or numb
- See – vision all or partially lost
- Feel – severe HA

- Any of these, call 911

Act F.A.S.T.

- **F**ACE
  - Ask the person to smile.
  - Does one side of the face droop?
- ARMS
  - Ask the person to raise both arms.
  - Does one arm drift downward?
- **S**PEECH
  - Ask the person to repeat a simple sentence.
  - Are the words slurred? Can he/she repeat the sentence correctly?
- **T**IME
  - If the person shows any of these symptoms, time is important.
  - Call 911 or get to the hospital fast. Brain cells are dying.

FAST


FACE
Has their face fallen on one side? Can they smile?
ARMS
Can they raise both arms and keep them there?
SPEECH
Is their speech slurred?
TIME
999
Time to call 999 if you see any single one of these signs.

Signs of Strokes: Get to Emergency Room

- Time lost is brain function lost

- For each hour lost, brain loses:
  - 120 million neurons,
  - 830 billion synapses,
  - 714 km (447 miles) of myelinated fibers

Time is crucial = Neuron loss in Stroke

- In acute stroke, “time is brain”:
  - irreversible neuronal damage is rapid;
  - early intervention can lead to improved outcomes.

- The average duration of nonlacunar stroke evolution is 10 hours (range 6 to 18 hours)

- In each minute,
  - 1.9 million neurons,
  - 14 billion synapses,
  - and 12 km (7.5 miles) of myelinated fibers are destroyed.

Signs of Strokes: Get to ED

- Time lost is brain function lost:

- Each hour lost: 120 million neurons, 830 billion synapses, and 714 km (447 miles) of myelinated fibers are lost

- Warning signs:
  - a sudden numbness, especially at one side of the body;
  - sudden trouble speaking or seeing;
  - loss of balance or sudden vertigo;
  - sudden severe headache with no apparent cause

Time = Neuron loss in Stroke

- In acute stroke, “time is brain”: irreversible neuronal damage is rapid; early intervention can lead to improved outcomes.
- The typical final volume of large vessel, supratentorial ischemic stroke is 54 mL (varied in sensitivity analysis from 19 to 100 mL).

- The average duration of nonlacunar stroke evolution is 10 hours (range 6 to 18 hours), and the average number of neurons in the human forebrain is 86 billion.

- In patients experiencing a typical large vessel acute ischemic stroke, 120 million neurons, 830 billion synapses, and 714 km (447 miles) of myelinated fibers are lost each hour.

Time and Stroke 2

- In each minute, 1.9 million neurons, 14 billion synapses, and 12 km (7.5 miles) of myelinated fibers are destroyed.
- Luckily you have 186 billion brain cells & 10 trillion synapses

- Compared with the normal rate of neuron loss in brain aging, the ischemic brain ages 3.6 years each hour without treatment.

- CONCLUSIONS: Quantitative estimates of the pace of neural circuitry loss in human ischemic stroke emphasize the time urgency of stroke care.

- The typical patient loses 1.9 million neurons each minute in which stroke is untreated.

Stroke, Jan 2006: 37, 263

Cerebral Infarctions Are Very Common in Older People

- The most important cerebrovascular pathology that contributes to cognitive impairment is cerebral infarcts (area of necrotic tissue).
- Cerebral infarcts are discrete regions of tissue loss observed by the naked eye (macroscopic) or under the microscope (microscopic).
- Chronic macroscopic infarcts are very common, occurring in approximately one third to one half of older people, a frequency far greater than the frequency of clinical stroke
- Larger volumes and an increased number of macroscopic infarcts are associated with an increased likelihood of dementia

Stroke: causes by age

- Adult
  - Atherosclerosis
  - Emboli (cardiac and noncardiac)

- Young Patient
  - Arterial dissection
  - Vasculopathy
  - Emboli
  - Drug abuse
  - Venous Thrombosis
  - Blood dyscrasia (abnormal cells)

Pathophysiology

- Brain gets 15-20% of oxygenated blood pumped from heart.

- Grey matter CBF is 80 ml/100gm/min; 3-4 x that of white matter CBF; mean CBF of 60/100
- Blood brings glucose and oxygen and disperses heat and metabolic byproducts
- Severe ischemia produces infarction
- Infarct: localized necrosis is resulting from obstruction of the blood supply

Pathophysiology of a stroke

- Blood supply to a specific part of the brain is disrupted and it does not receive adequate oxygen or glucose.
- After several minutes, an infarct is created (necrosis; dead or damaged tissue)
- Two prominent types:
  - Ischemic (obstructive)
  - Hemorrhagic (bleed)

Ischemic strokes

- Acute ischemic stroke is characterized by the sudden loss of blood circulation to an area of the brain, typically in a vascular territory, resulting in a corresponding loss of neurologic function.

- 82%-92% of strokes are ischemic.

- 80% preventable

Epidemiology

- Ischemic stroke: 5 per 1000 per year in 45 years +
- Age: 2 cases per 1000 in 45-54; 20 cases per 1000 in 85+
- 9.7% of deaths; fourth most common case of death (after heart disease, CA, lung)
- Causes death in 12-20% of cases within 1 month of stroke
- 80% preventable

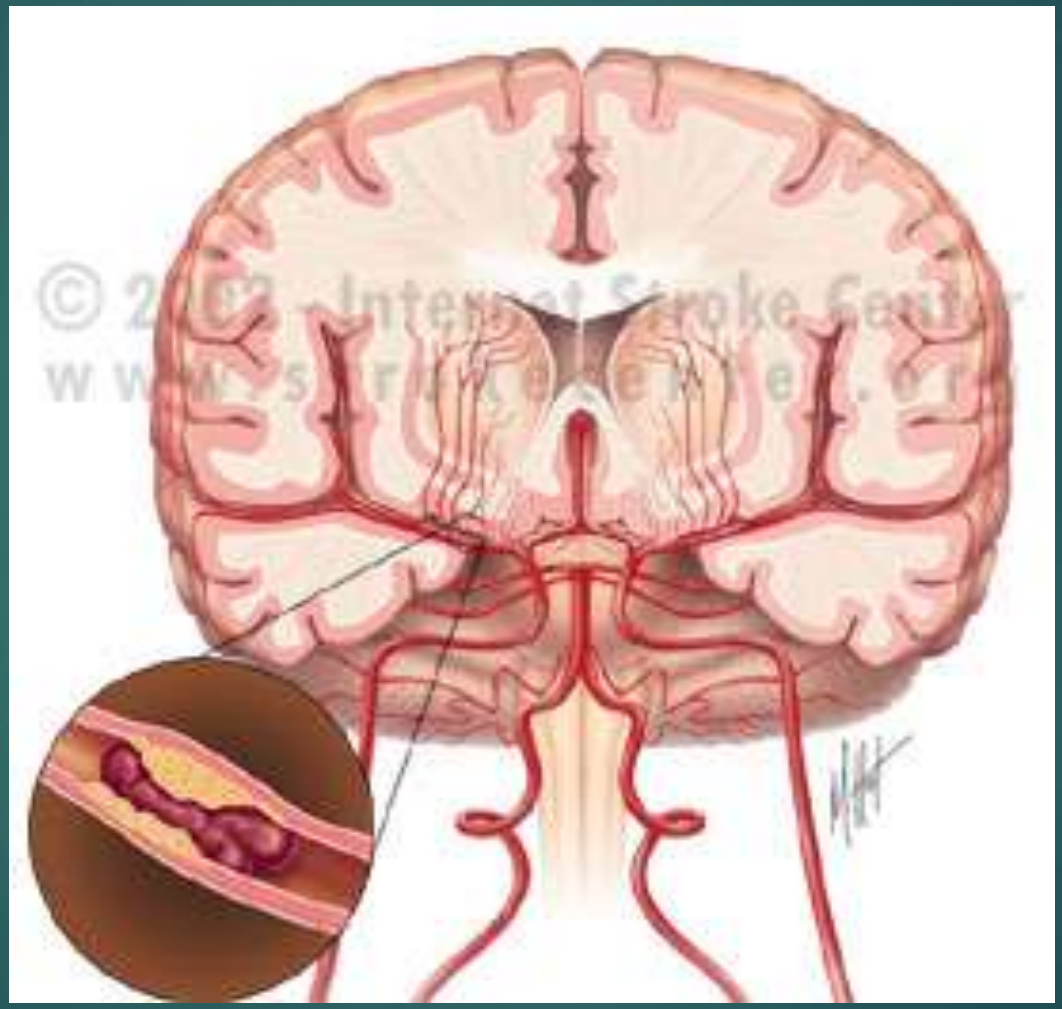
Ischemic Infarction: no Oxygen

- Ischemia: decrease of blood supply to the brain; CBF fails to meet oxygen requirements of brain
- Whenever blood flow through arteries is blocked sufficiently to cause cell death.
- When perfusion drops 20%, cell death occurs
- Atherosclerosis:
  - Etiology when 50% stenosis of an artery
  - Via embolization of plaque fragment or obstruction of CBF, therefore low perfusion

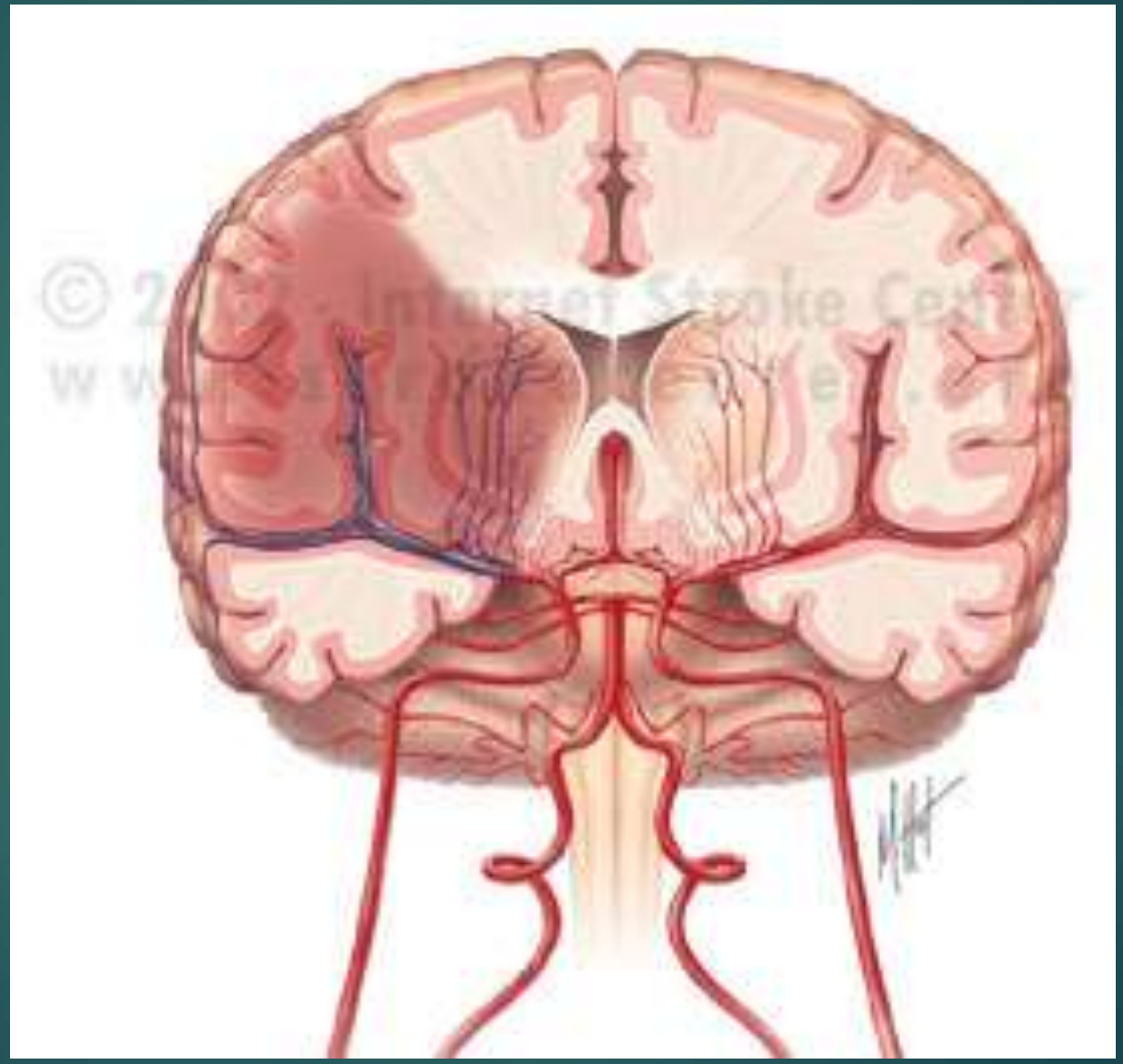
Types of stroke/Etiology

- Ischemic (obstructive) strokes (80% of all strokes); caused by blockage of a vessel
  - Cerebral thrombosis (block)
  - Cerebral embolism (break away)
  - Cerebral atherosclerosis
  - Cerebral vasculitis

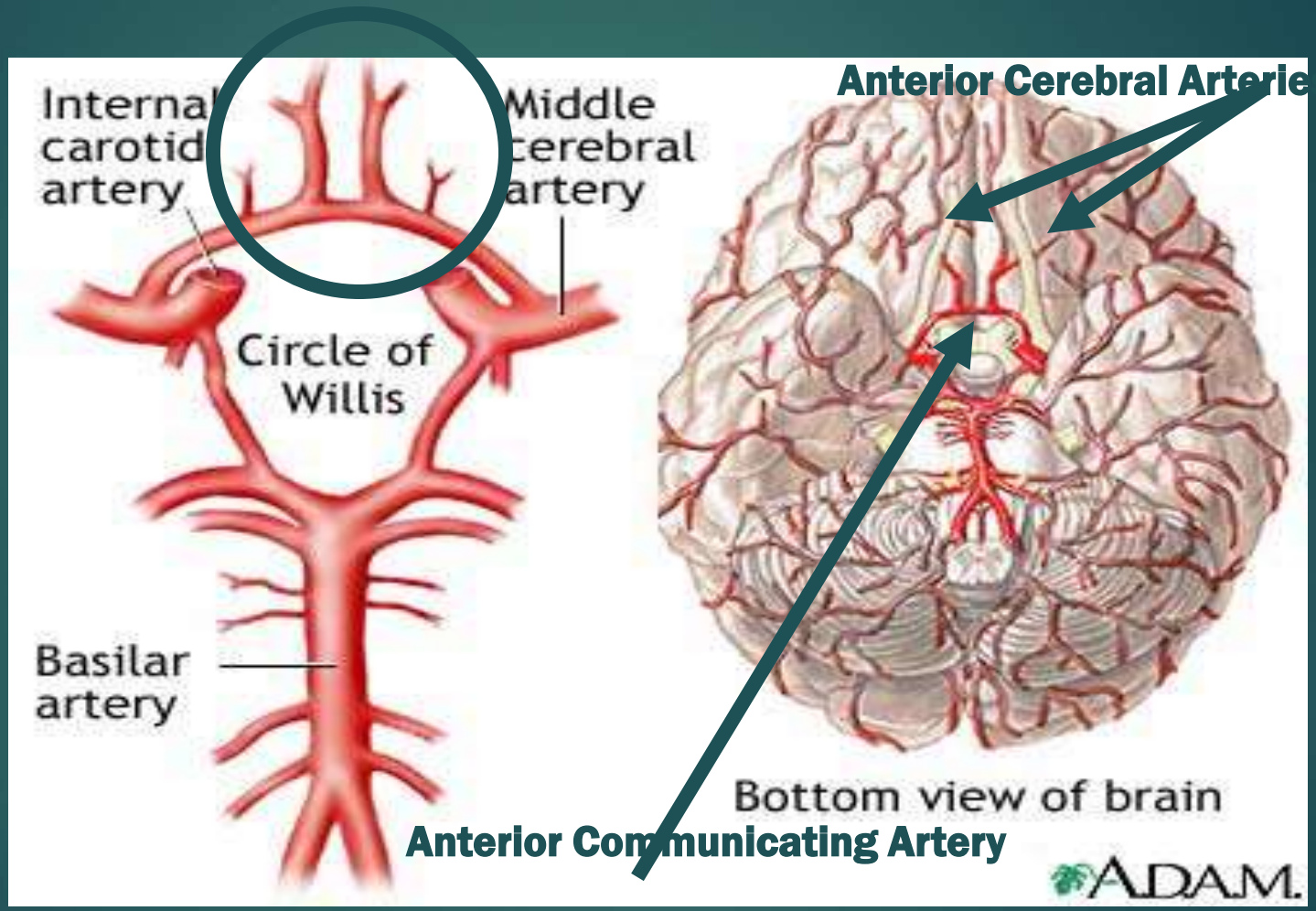
Ischemic stroke



Damage from ischemic stroke



Frontal Lobe Dysfunction in stroke



70% of all ischemic strokes occur in the anterior circulation.

Cerebral Thrombosis

- Obstruction due to buildup of atherosclerotic plaques, which are fat deposits within the artery walls.
- Accounts for 50-70% of all strokes.
- Results from accumulation of coagulated blood, plugs of tissue, or plaques *that remain at the point of formation*.

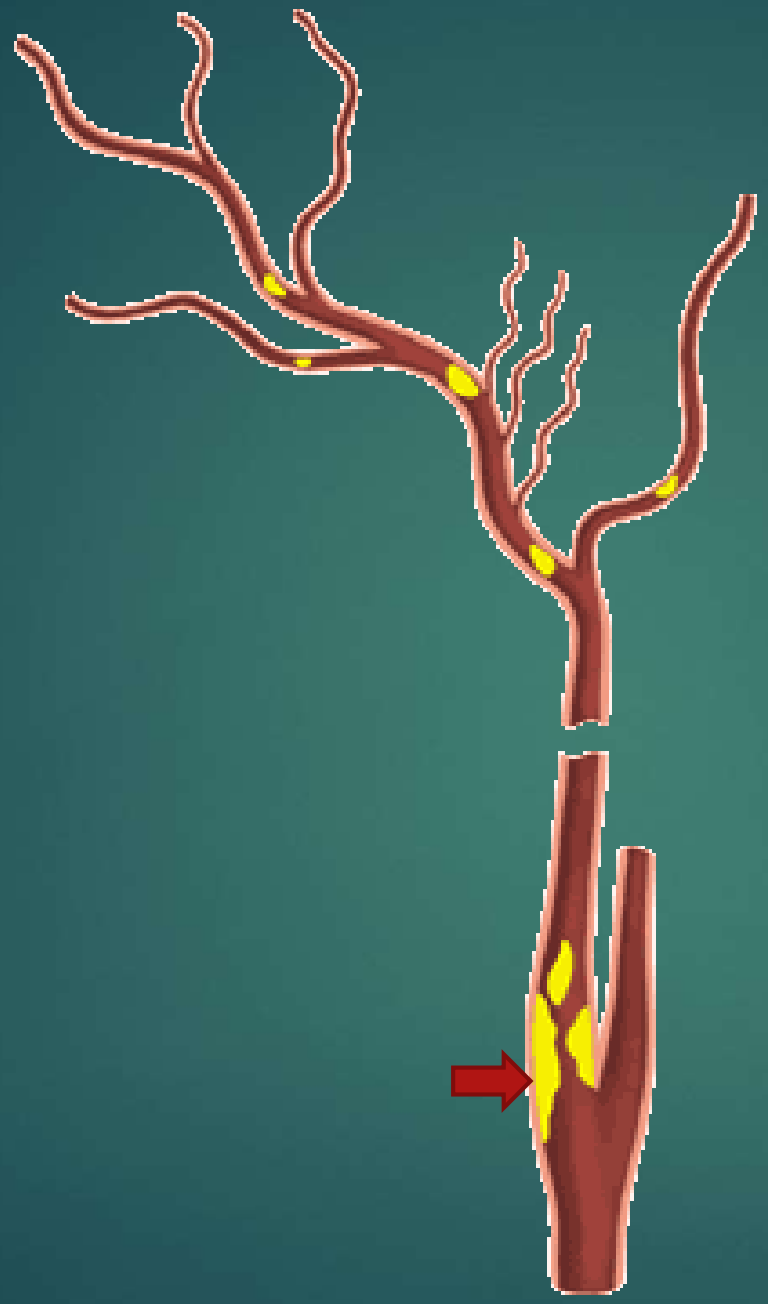
Cerebral Thrombosis 2

- Usually happens where blood vessels branch or at lesion sites on the vessel walls.
- Usually occur suddenly, but often take 1/2 hour to develop fully.
- Occasionally (up to 1/3 of cases) evolve for hours or days.
- Often preceded by TIA's (50-80% of cases)

Cerebral Thrombosis 3

- Large-vessel thrombosis
  - Evolve from plaques in internal carotid and vertebral arteries that travel to middle cerebral or vertebral basilar artery. 30% of all strokes
- Small-vessel thrombosis
  - Small, deeply penetrating arteries (e.g., lenticulostriate, basilar penetrating, medullary), account for 20% of all strokes, cause *lacunar strokes*
- MCA: affect posterior frontal, temporal, and parietal structures
- VBA: brain stem, inferior temporal lobe (incl. hippocampus), and occipital lobes.

Emboli



Cerebral embolism

- Blockage of a blood vessel by abnormal particle circulating in the blood

- Embolus: a plug of thrombus material or fatty deposit *broken away* from blood vessel walls or plug of foreign matter (clumps of bacteria, gas bubbles).
- Emboli travel from heart or arteries: platelet aggregates, calcium particles, cholesterol crystals, air, fat

- 20-30% of strokes are embolic in nature; Predilection for middle cerebral artery
- Tend to have abrupt onset without warning precursors such as TIA or headache

Embolic disease

- Emboli travel from heart or arteries: platelet aggregates, calcium particles, cholesterol crystals, air, fat
- Frequent nonprogressive acute onset, diminished level of csness, hemianopia without hemiparesis/sensory loss, Wernicke's aphasia, ideomotor apraxia
- Predilection for middle cerebral artery

Cerebral embolism 2

- Tend to have abrupt onset without warning precursors such as TIA or headache
- 5 to 6% begin with fluctuating and evolving symptoms over a day or two
- Middle cerebral artery most common site

Cerebral atherosclerosis

- Obstruction can occur when narrowing of the vessel results from thickening and hardening of the arteries

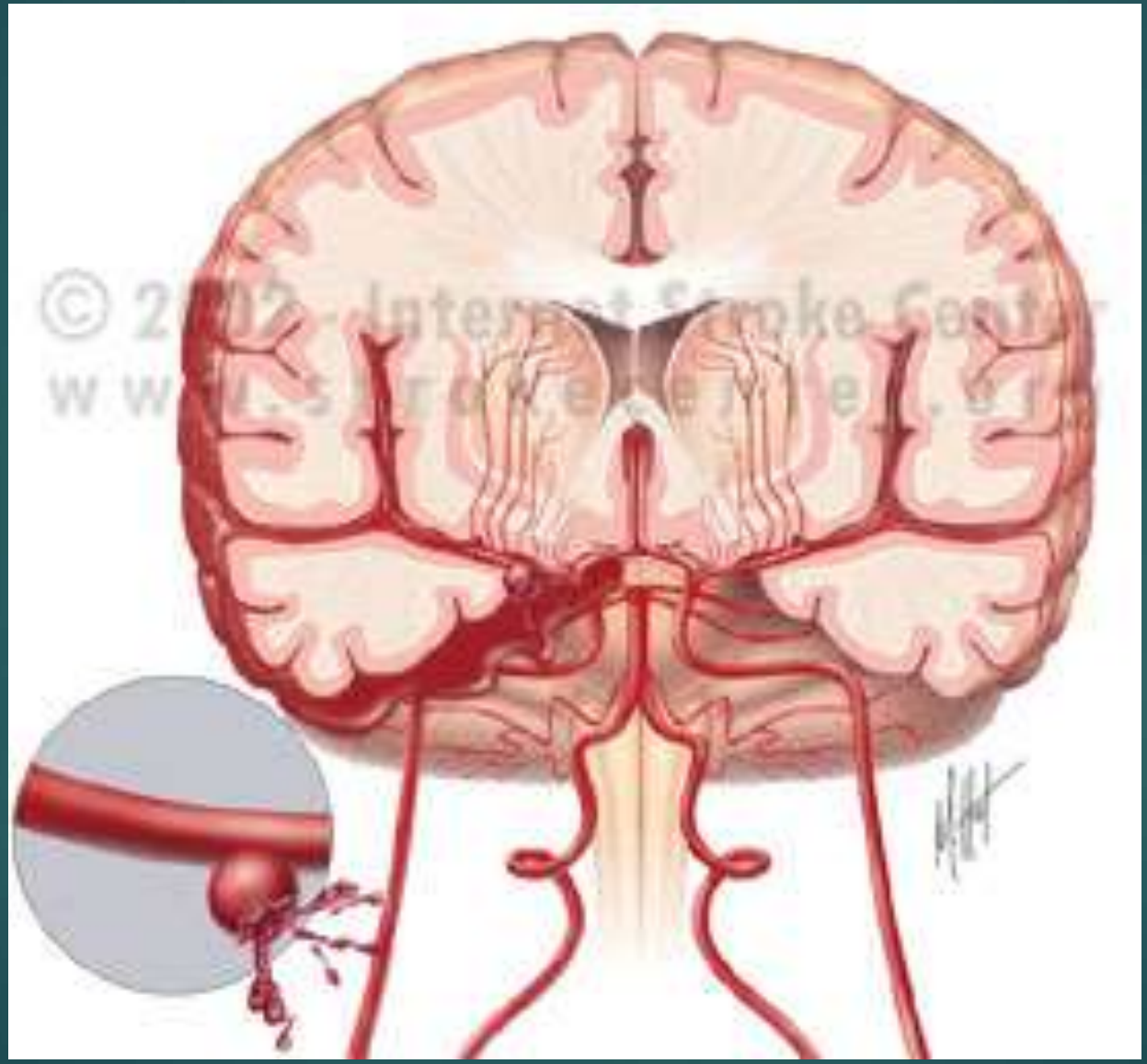
Cerebral vasculitis

- Inflammation or vasospasm (spasmodic contraction of blood vessels) can cause narrowing of the vessels and restriction of the blood supply

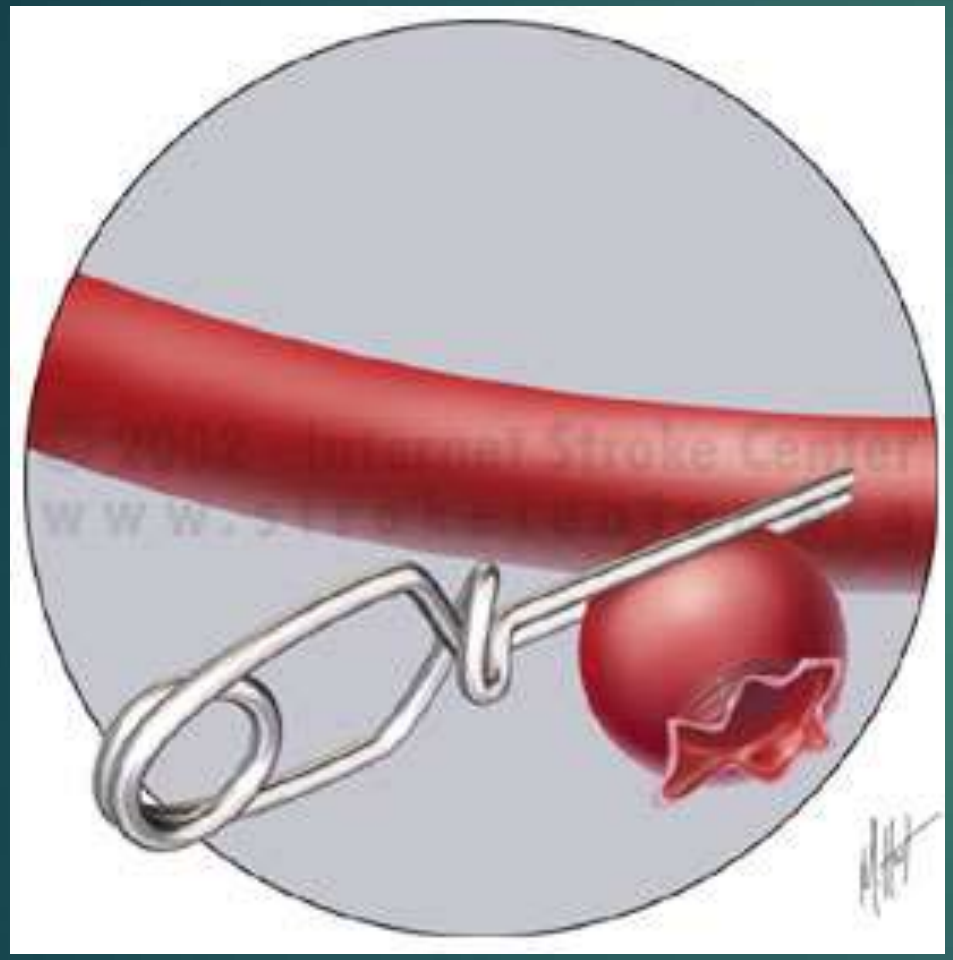
Hemorrhagic Stroke

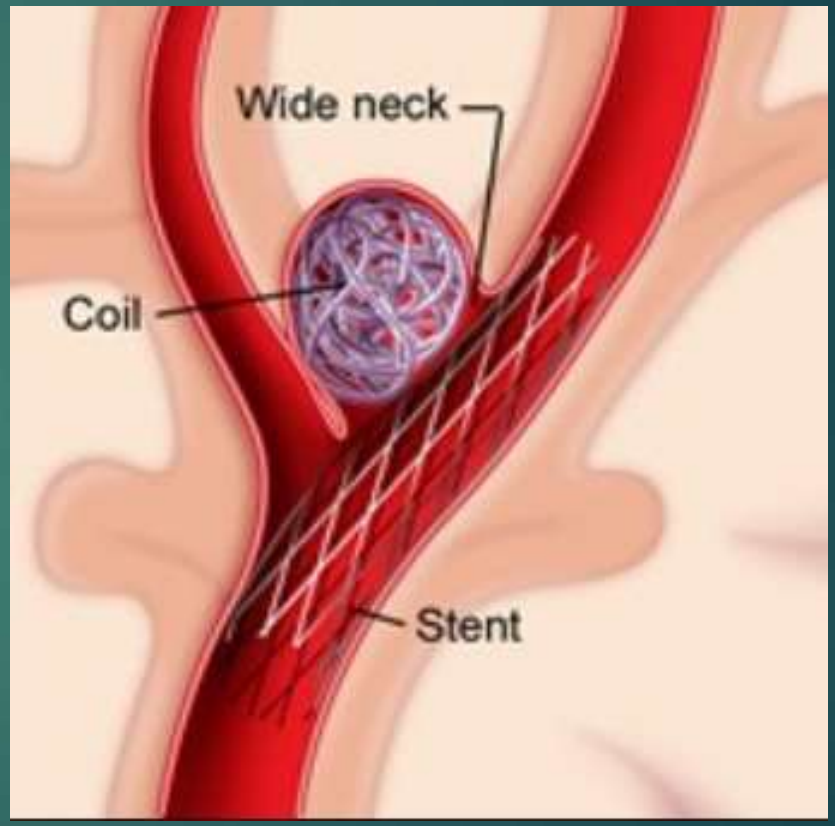
- Rupture of a blood vessel: a non-traumatic bleeding into the brain; classified by location; Accounts for 12% of all strokes
- Due to
  - hypertension (the major risk factor for intracerebral)
  - arteriovenous malformations (AVM); major risk factor for subarachnoid
  - tumors,
  - Improper use of anti-coagulants,
  - speed/stimulants,
  - ruptured aneurysm (branch points of circle of Willis): common cause of subarachnoid hem.)
  - epidural/subdurals due to trauma

Subarachnoid hemorrhage



Aneurysm clipping & coiling





Warning signs of hemorrhagic stroke

- Painful headaches
- Nausea and vomiting
- Focal neurologic signs

Silent strokes

- Strokes that go unnoticed until CT or MRI reveals them; 11%
- Tend to be small, lacunar lesions situated deep in brain structures; esp. Basal Ganglia
- Sudden change of behavior in an elderly person may be caused by a silent stroke

Cerebrovascular disease–associated brain injury (CVBI): Silent strokes & WML

- Estimates of the prevalence of silent cerebral infarction on MRI in community-based samples vary between 5.8% and 17.7%, with an average of 11%

- Most have a single lesion, and the infarcts are most often located in the basal ganglia (52%), followed by other subcortical (35%) and cortical (11%) areas

- White matter lesions (WMLs) are even more common and are generally present in most people 30 years of age, increasing steadily in extent with advancing age.

Silent Strokes in Middle Age

- About 10 percent of the apparently healthy middle-aged participants with no symptoms of stroke were injured from "silent strokes."
- N = 2000, MRIs, Framingham Offspring Study (children of participants in the original Framingham Heart Study).
- Among patients who displayed no symptoms of stroke, 10.7 percent had SCIs on routine brain MRI
- Of those in the study with SCIs, 84 percent had a single lesion.

Mini Strokes Cause Mega Problems for Brain Cleansing

- Microinfarcts heighten risk for Alzheimer’s
- Tiny infarcts disrupt glymphatic clearance throughout the brain, allowing toxic waste to stick around and inflame surrounding tissue.

Outcome of Strokes

- 26% of 1st ever stroke had impaired MS 1 month following; 21% at 6-12 months
- 35% have cognitive impairment
- Dependent living if cog. impairment
- Level of cog decline at 3 months predicts that at 12 months
- Predictors of dependency include sustained attention, praxis, emot. control, and memory

Outcome statistics for stroke survivors

- 20% live in SNFs or private hospitals
- 50% live without institutional care (with assistance)
- Only 30% remain independent in ADLs
- Pts w/stroke account for more hospital and SNF bed days than any other condition
- Lifetime costs range from $59,800 to $230,000 per stroke patient

(Barker-Collo & Feigin, 2006)

Southern Stroke Belt

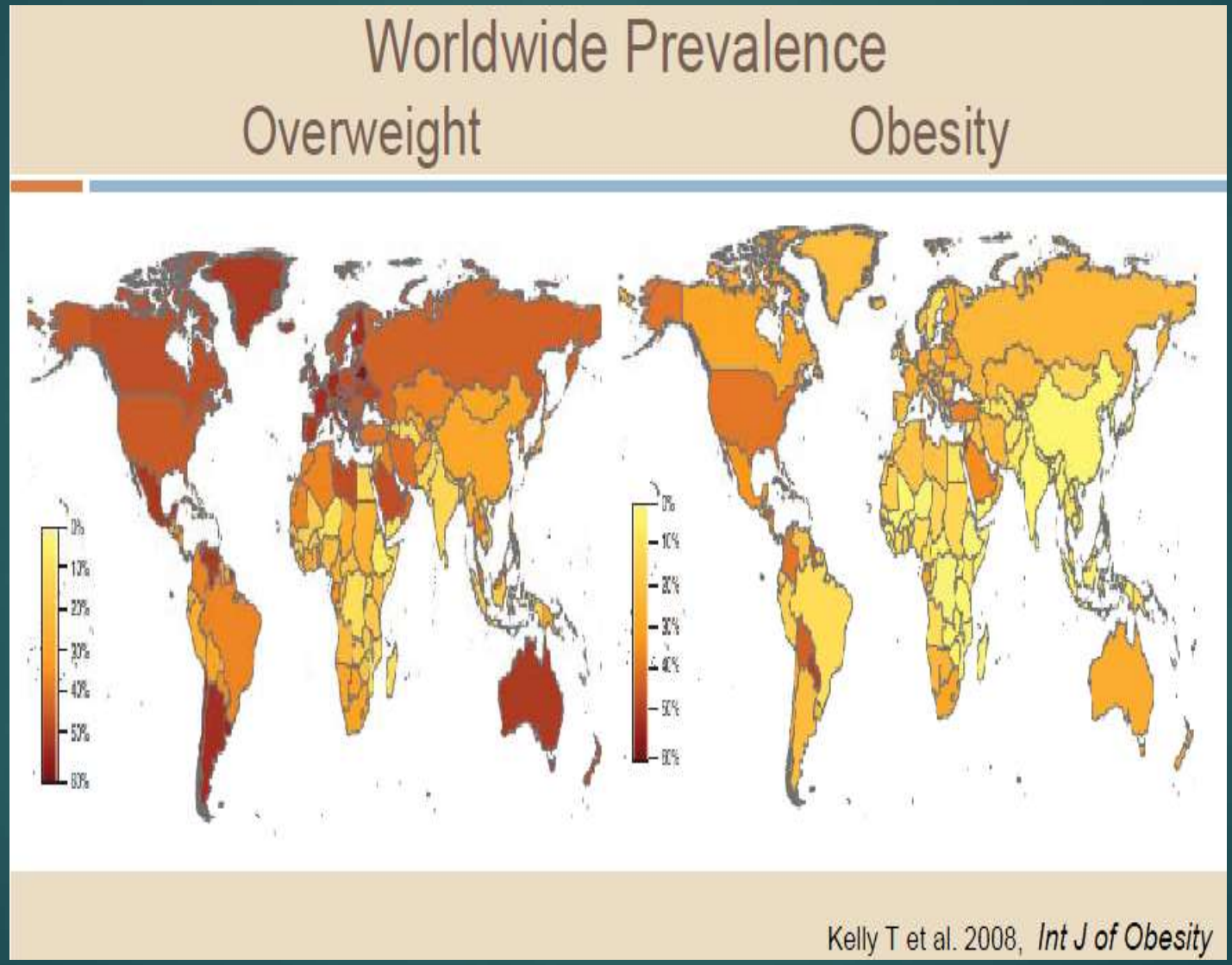
- People born in the Southern "stroke belt" (NC, SC, TN, AR, MS and AL) have a higher risk of dying from stroke as adults, even if they later move away.

- People who live in the stroke belt in adulthood also had elevated risk of dying from stroke, even if they were not born there.

- Also higher rates of CV disease, and cognitive deficits.

- Higher rates of hypertension, low SES, high fat diet, cultural lifestyle, quality of health care facilities, smoking, and infections.

Obesity


Worldwide Prevalence
Overweight
Obesity
Kelly T et al. 2008, Int J of Obesity

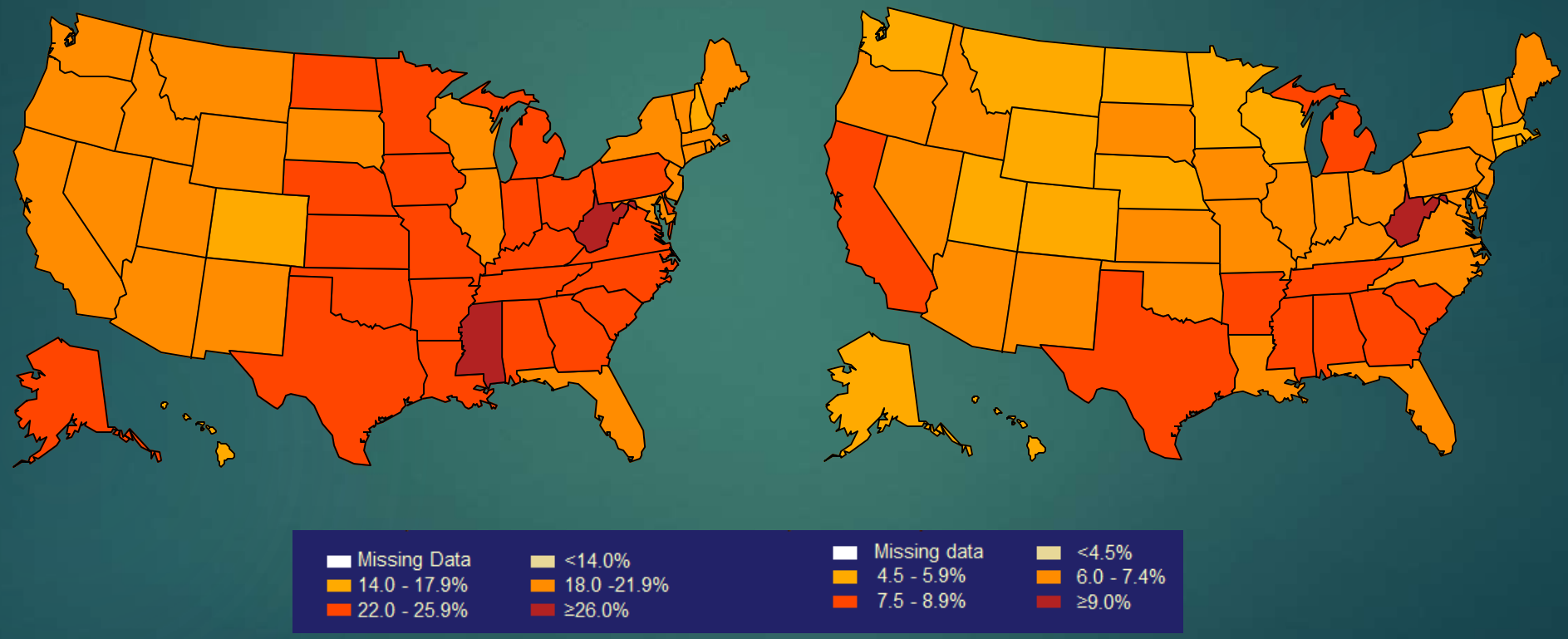
We are overweight

- 50% of US adults are overweight
- 22% of US adults are obese (30 lbs.)

Run 1 mile = 100 calories

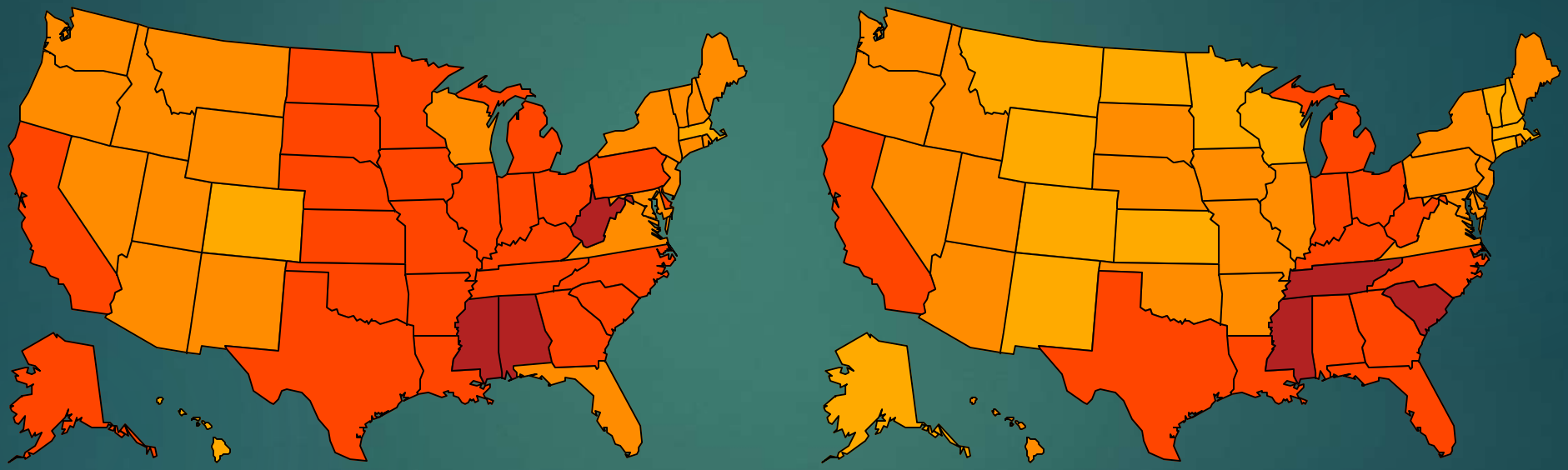
Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

2002

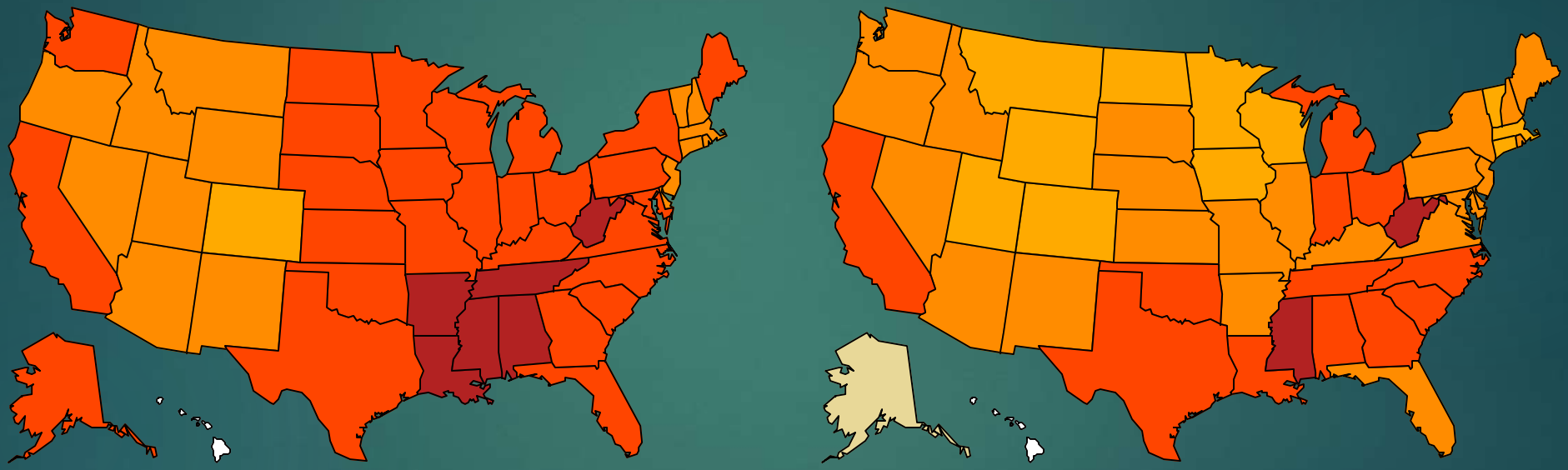


Obesity **Diabetes**

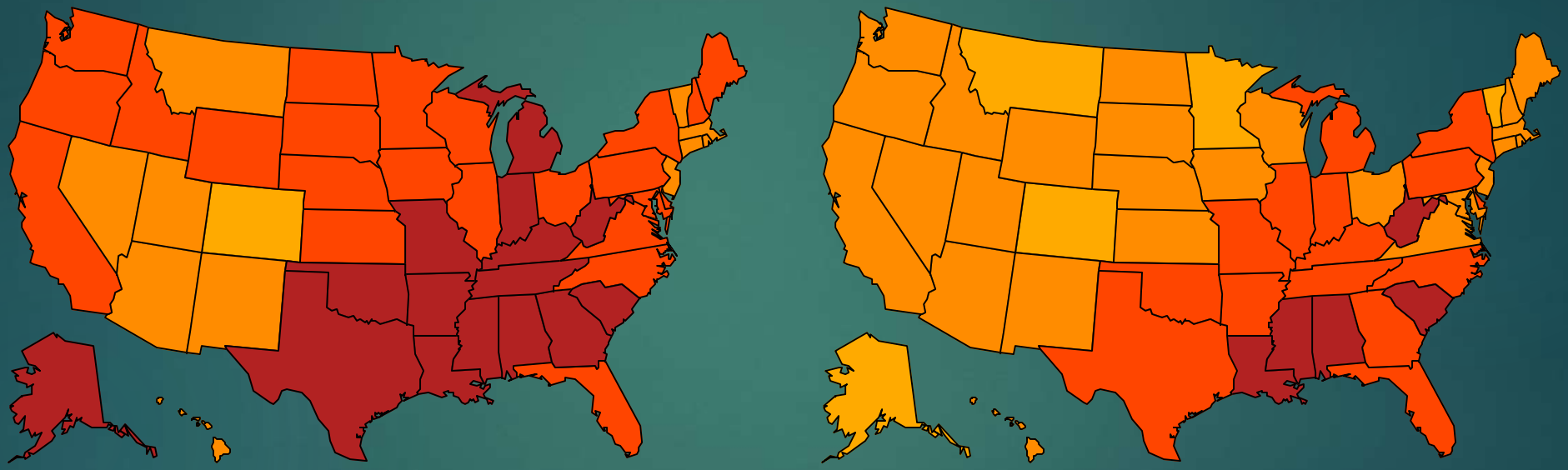
2003



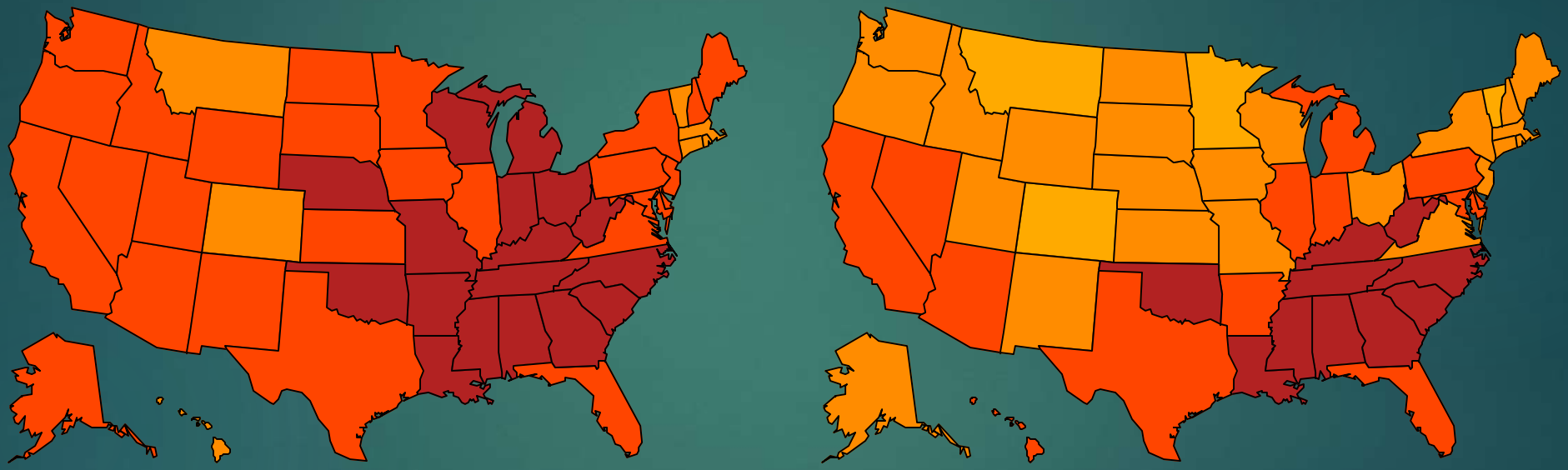
2004



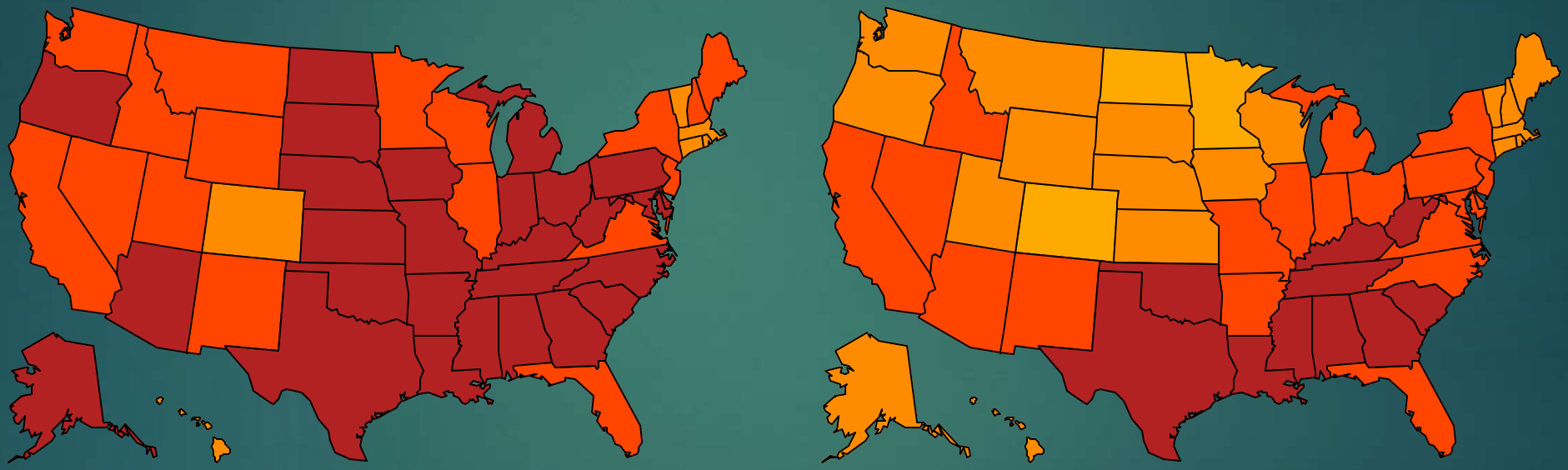
2005



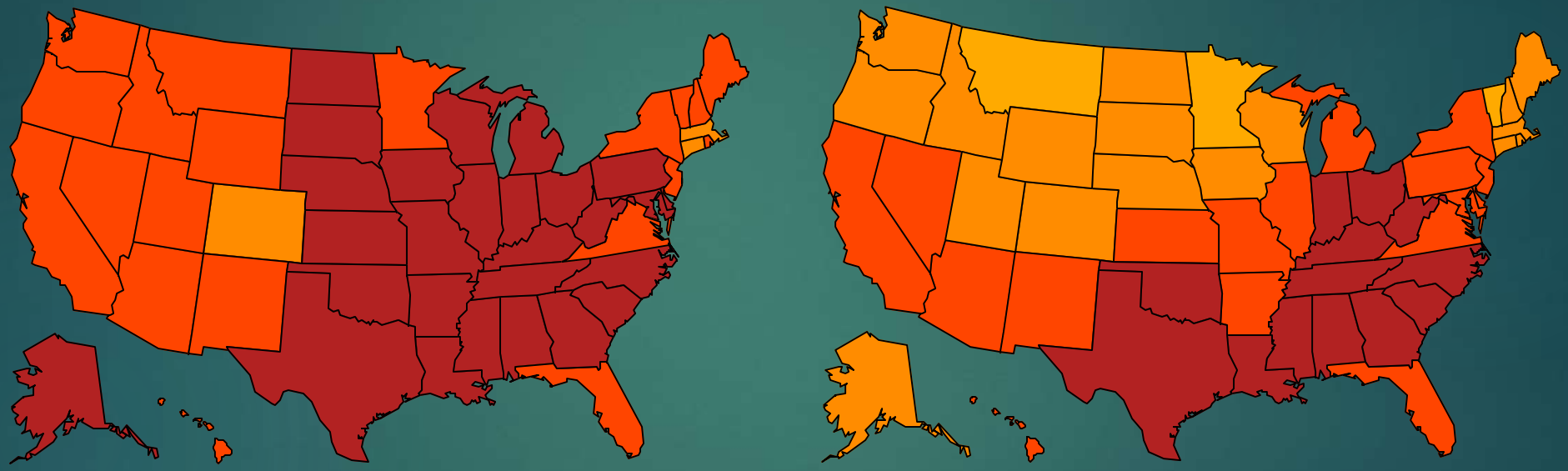
2006



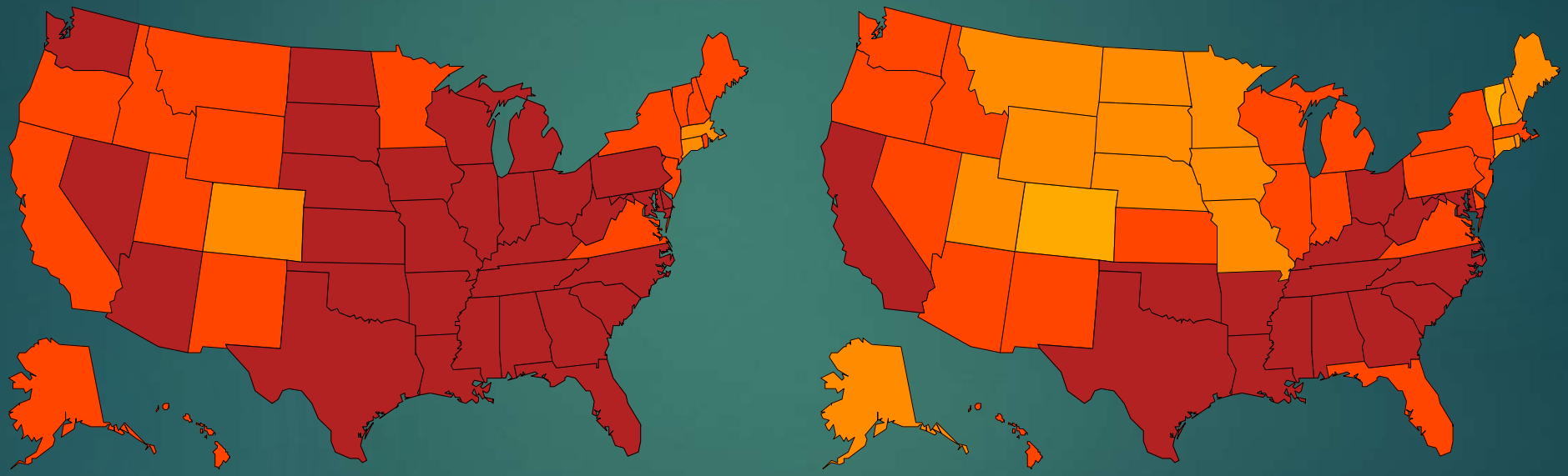
2007



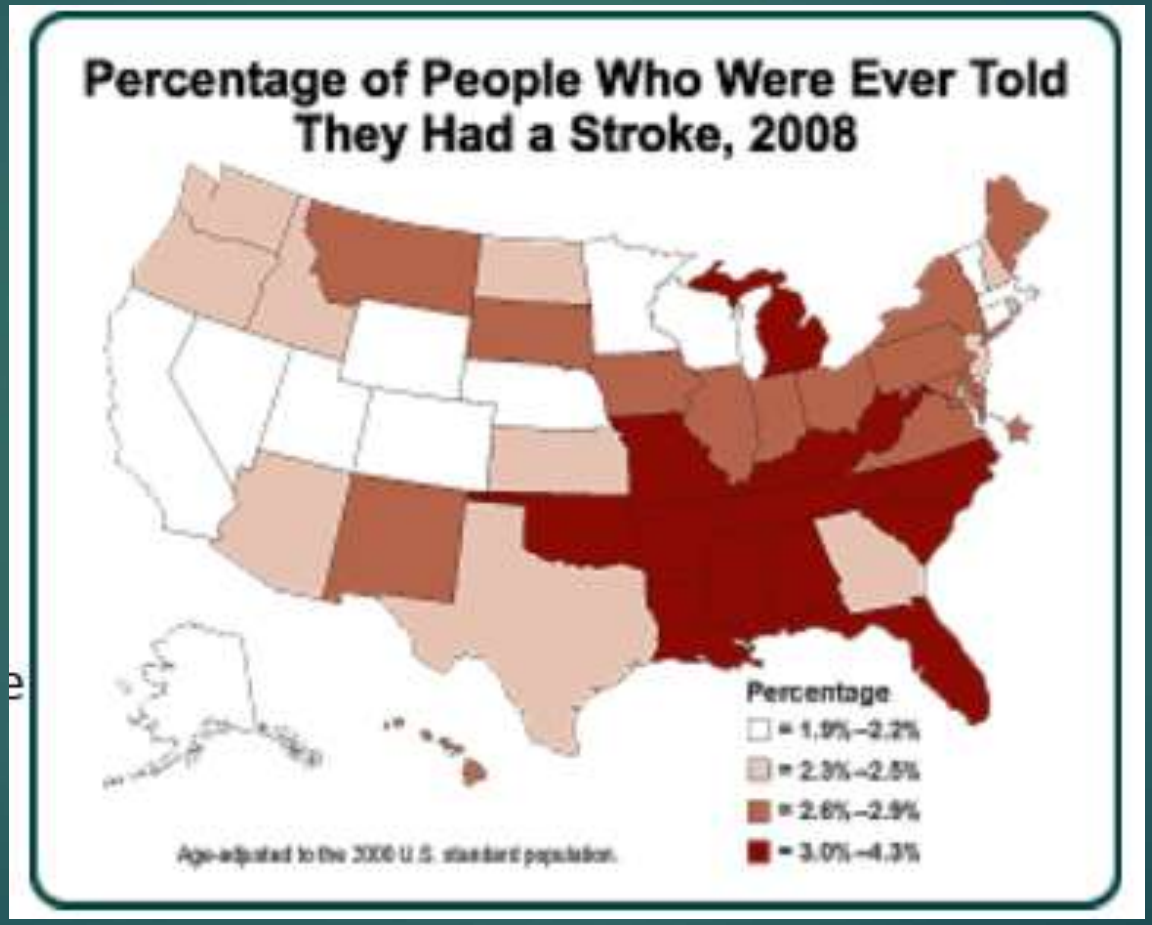
2008



2009

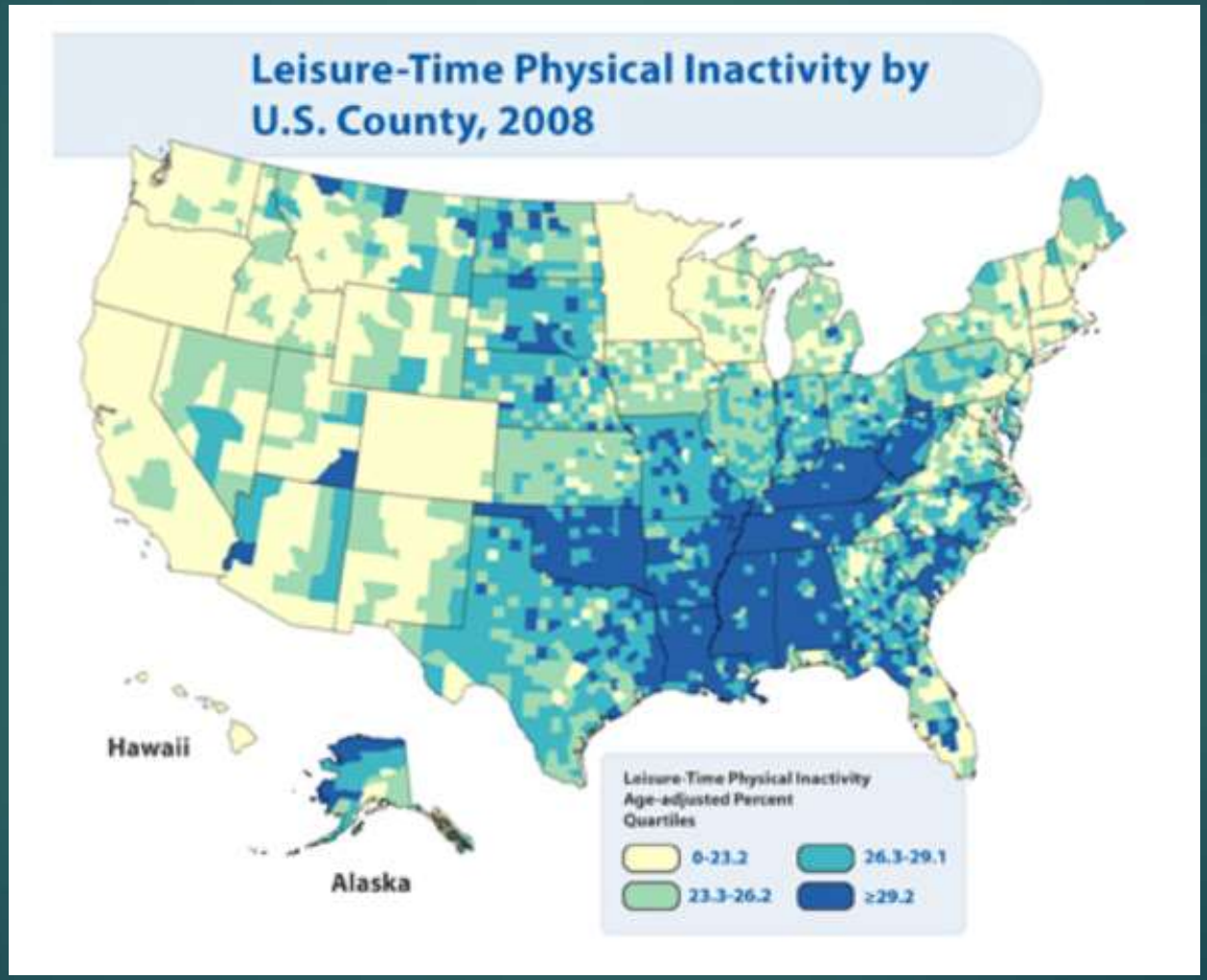


CDC % Stroke



Highly tied to high consumption of fried and processed foods

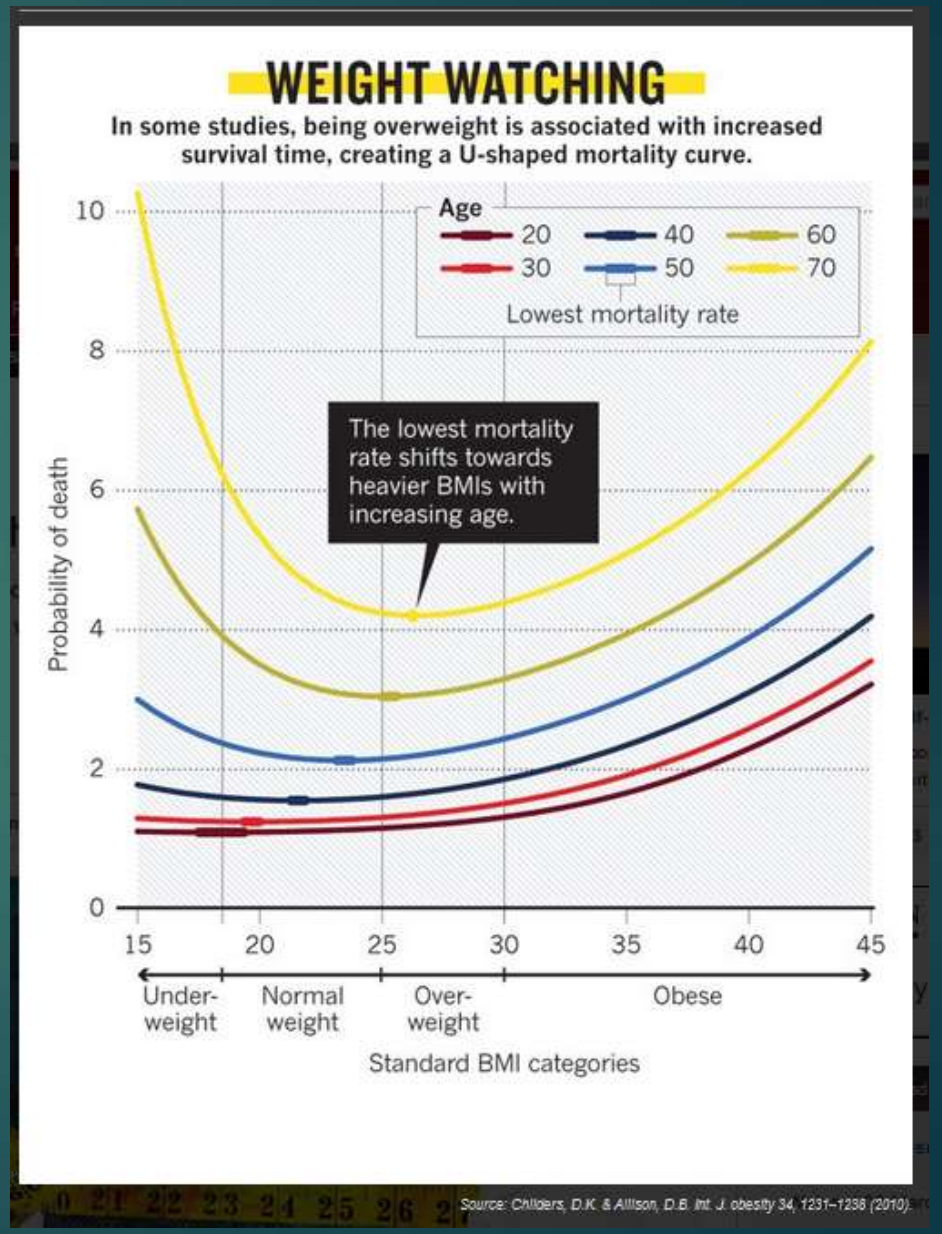
CDC Physical Inactivity



The obesity paradox: With age, lower death rates with higher BMIs

- Meta-analysis of 97 studies including 2.88 million people
- People deemed 'overweight' were 6% less likely to die than were those of 'normal' weight over the same time period
- Paradox: Being overweight increases a person's risk of diabetes, heart disease, cancer and many other chronic illnesses.
- But for some people — particularly those who are middle-aged or older, or already sick — a bit of extra weight - but not obesity - is not particularly harmful.
- Metabolic reserves could be important as people age.

Katherine Flegal, et al. 2014



Risk factors for Stroke

- 1 – Age: most important;

  after 55, risk doubles each decade

- 2 – Genetics
- 3 – Ethnicity:
  - African American (higher HTN, DM), Hispanics (DM, cholesterol)
  - AA, Hispanics, Asians > hemorrhagic
  - Influence of race decreases with age

Modifiable Risks for Strokes

- 4 – Hypertension: single most important, esp. for ischemic strokes
  - Even borderline HTN have 50% increase
  - 38% reduction in strokes in treated HTN
- 5 – Heart Disease
- 6 – DM: 4x greater risk; atherosclerosis accounts for 80% of mortality of DM pts

Modifiable Risks for Strokes

- 7 – Lipids ↑(cholesterol, LDL, HDL)
- 8 – BMI: association between BMI and Ischemic heart disease is continuous; any increase in BMI increases the risk of CVD; there is no threshold below which a BMI increase has no effect on CVD risk.

Depression increases Stroke Risk

- Depression is a risk factor for stroke
- LF Stroke often produces depression
- Risk is higher if have past hx of depression
- Treatment can improve both depression and cognitive effects.

Unfortunately so do Antidepressants

Antidepressant use is correlated with a 48% greater risk of stroke and that the magnitude of associations was greater in high-potency SSRIs (Paxil, Prozac).

- Why?
- Anti-depressant medication use may be an indicator of depression severity
- The medications themselves may not be the primary cause of the risk.

Sleep Apnea is a stroke risk

- Obstructive sleep apnea is associated with an increased risk of stroke in middle-aged and older adults, especially men.
- The risk of stroke appears in men with mild sleep apnea and rises with the severity of sleep apnea.
- Men with moderate to severe sleep apnea were nearly three times more likely to have a stroke.
- In women, however, the increased risk of stroke was significant only with severe levels of sleep apnea.

Susan Redline, 2010

Short Sleep

- Link between short cycles of sleep, stroke and silent cerebral infarct (SCI), or "silent strokes,"; in elderly hypertensive patients.

- Sleep duration less than 7.5 hours was independently associated with stroke risk

Stroke Presentation

- Consider stroke in any patient presenting with acute neurologic deficit or any alteration in level of consciousness. Common signs and symptoms of stroke include the abrupt onset of any of the following:
- • Hemiparesis, monoparesis, or (rarely) quadriparesis
- • Hemisensory deficits
- • Monocular or binocular visual loss
- • Visual field deficits
- • Dysarthria
- • Facial droop
- • Ataxia
- • Vertigo (rarely in isolation)
- • Aphasia
- Although such symptoms can occur alone, they are more likely to occur in combination.

Watershed Regions

Watershed cerebral infarction occurs at the border between cerebral vascular territories (ACA-MCA, MCA-PCA)

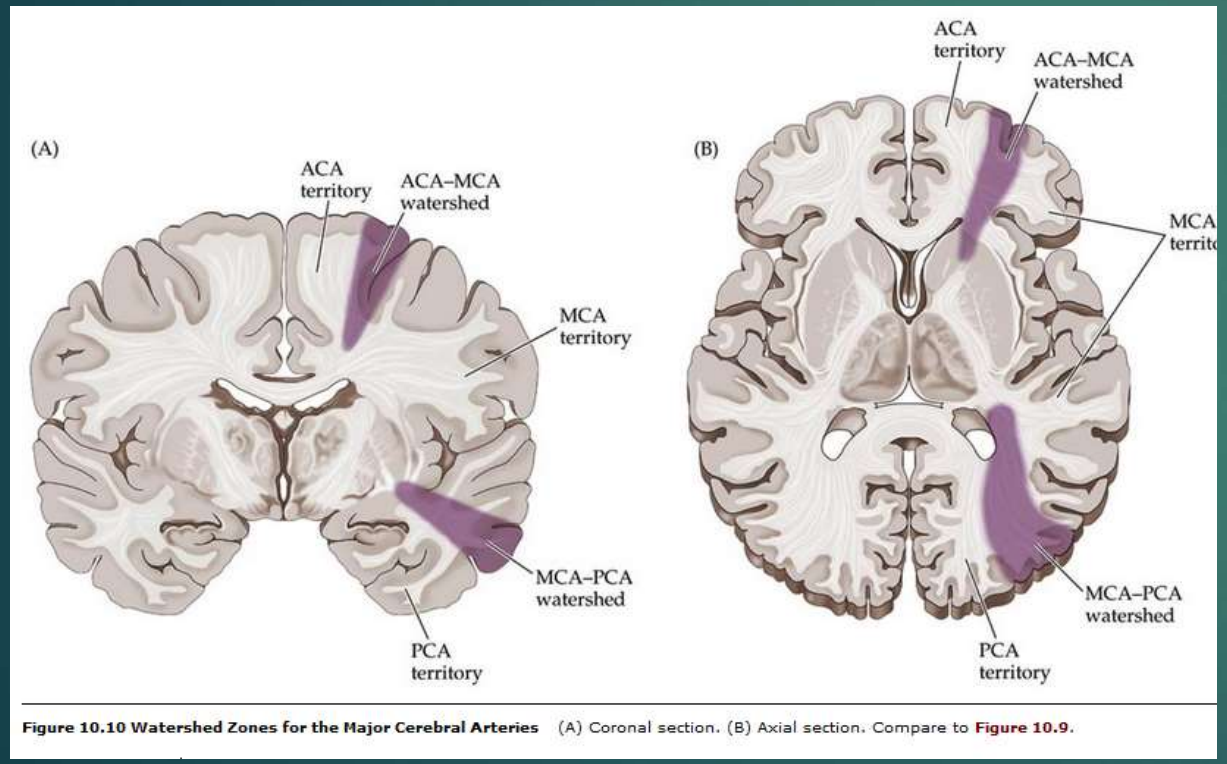
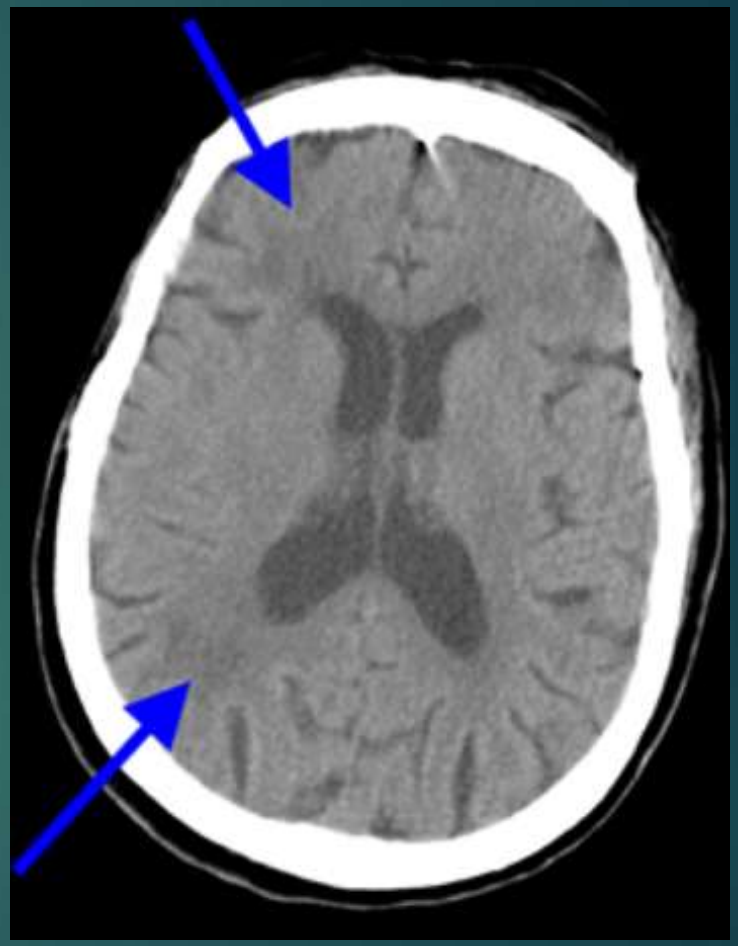


Figure 10.10 Watershed Zones for the Major Cerebral Arteries (A) Coronal section. (B) Axial section. Compare to **Figure 10.9.**



Watershed Infarcts

- Episode of transient global hypoperfusion may result in bilateral infarcts in watershed regions between arterial territories.

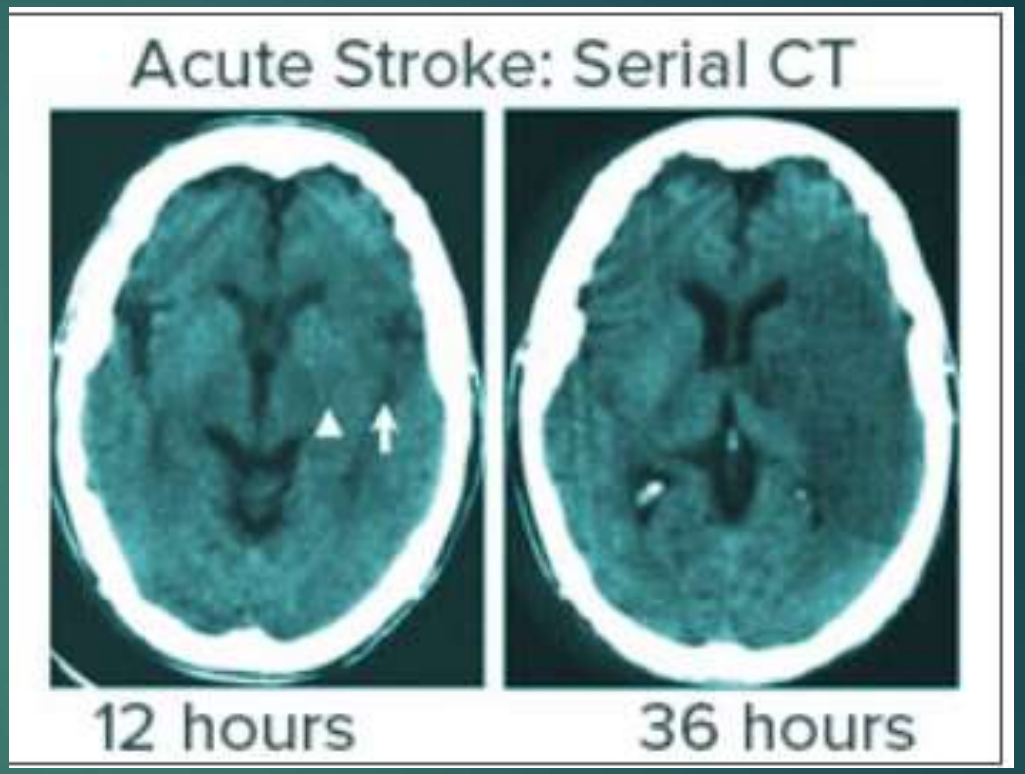
- Border zones between arteries are supplied by terminal branches. When flow to parent vessel decreases watershed brain is first to go.
- Cardiac arrest
- Anaphylaxis
- Massive bleed
- Surgery/Anesthesia

Cerebellar Stroke

- PICA, AICA, SCA
- Symptoms;
  - Headache, imbalance, dizziness, nausea, vomiting.
- Signs
  - Ataxia, nystagmus, dysarthria, neck stiffness

Evaluation of Stroke

- Noncontrast CT scanning is the most commonly used form of neuroimaging in the acute evaluation of patients with apparent acute stroke.



CT Signs of acute Stroke

- Minutes of Stroke (Hyperacute)
  - CT generally negative

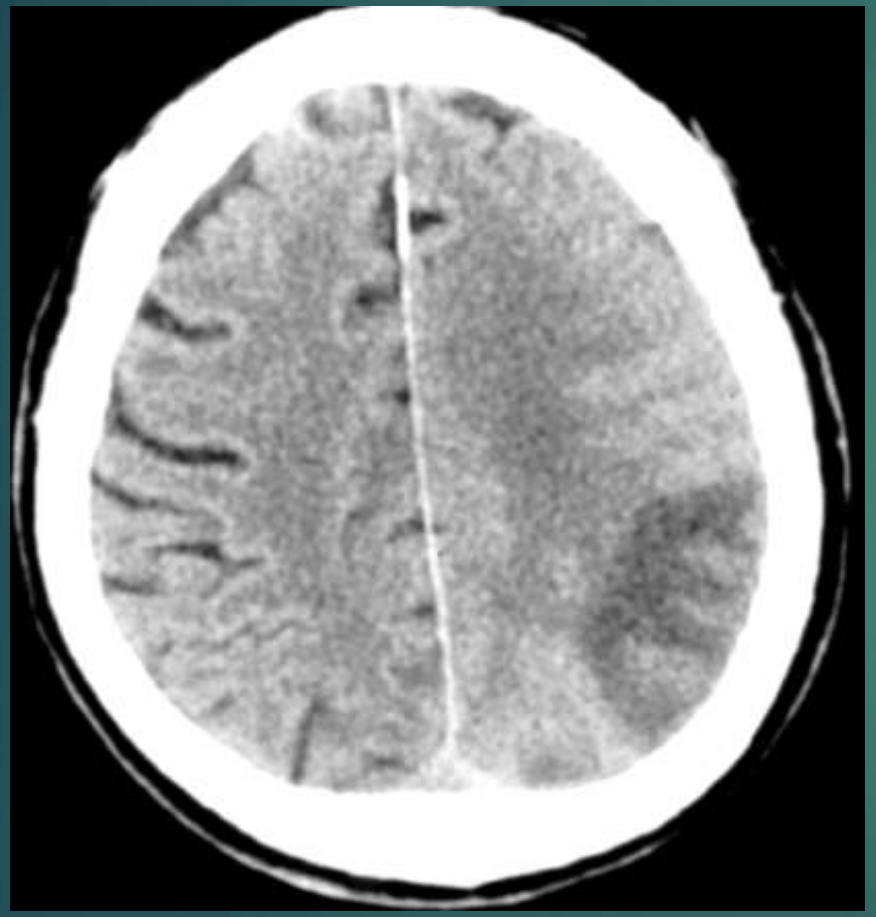
- Acute Period (2-6hrs)
  - Hyperdense Artery Sign
  - Insular Ribbon Sign
  - Lentiform nucleus sign

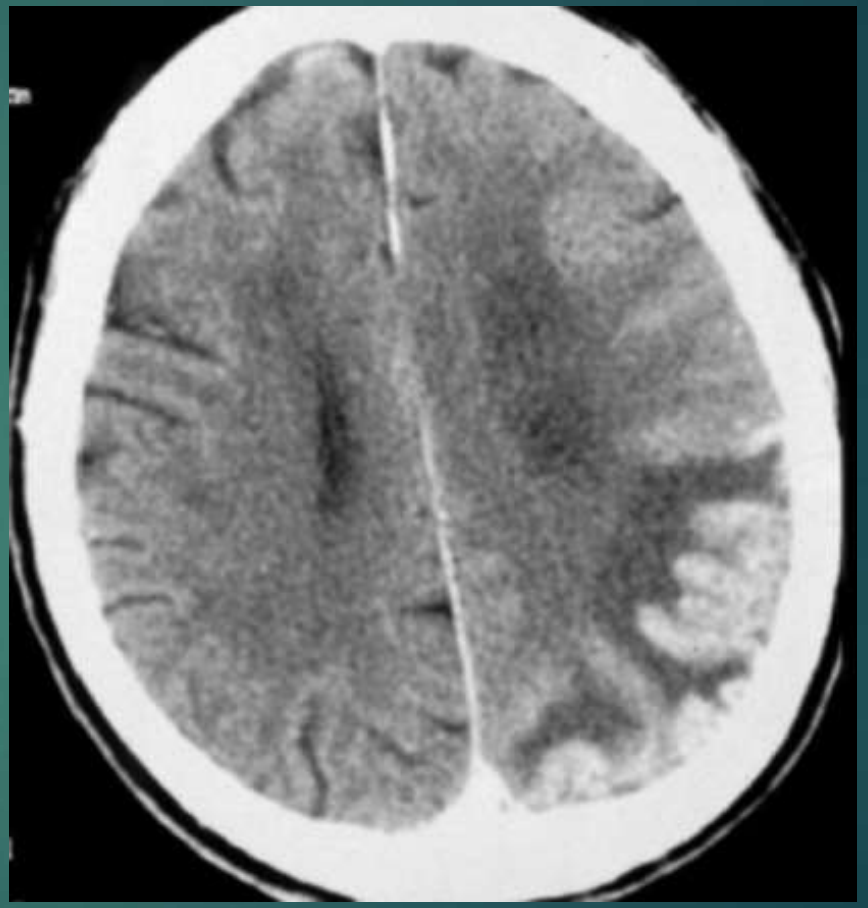
Subacute Period (6-12hrs)

Sulcal Effacement and low attenuation in region of infarct that extends to the periphery involving grey and white matter = cytoxic edema

CT Signs of acute Stroke

- 3-7days
  - Maximum edema
- 3-21 days
  - Petechial Hemorrhage-Hemorrhagic transformation
  - Correlates with BBB breakdown and Gyral enhancement
  - Rule of 3’s
    - Peaks 3 days to 3 weeks and resolves by 3 months



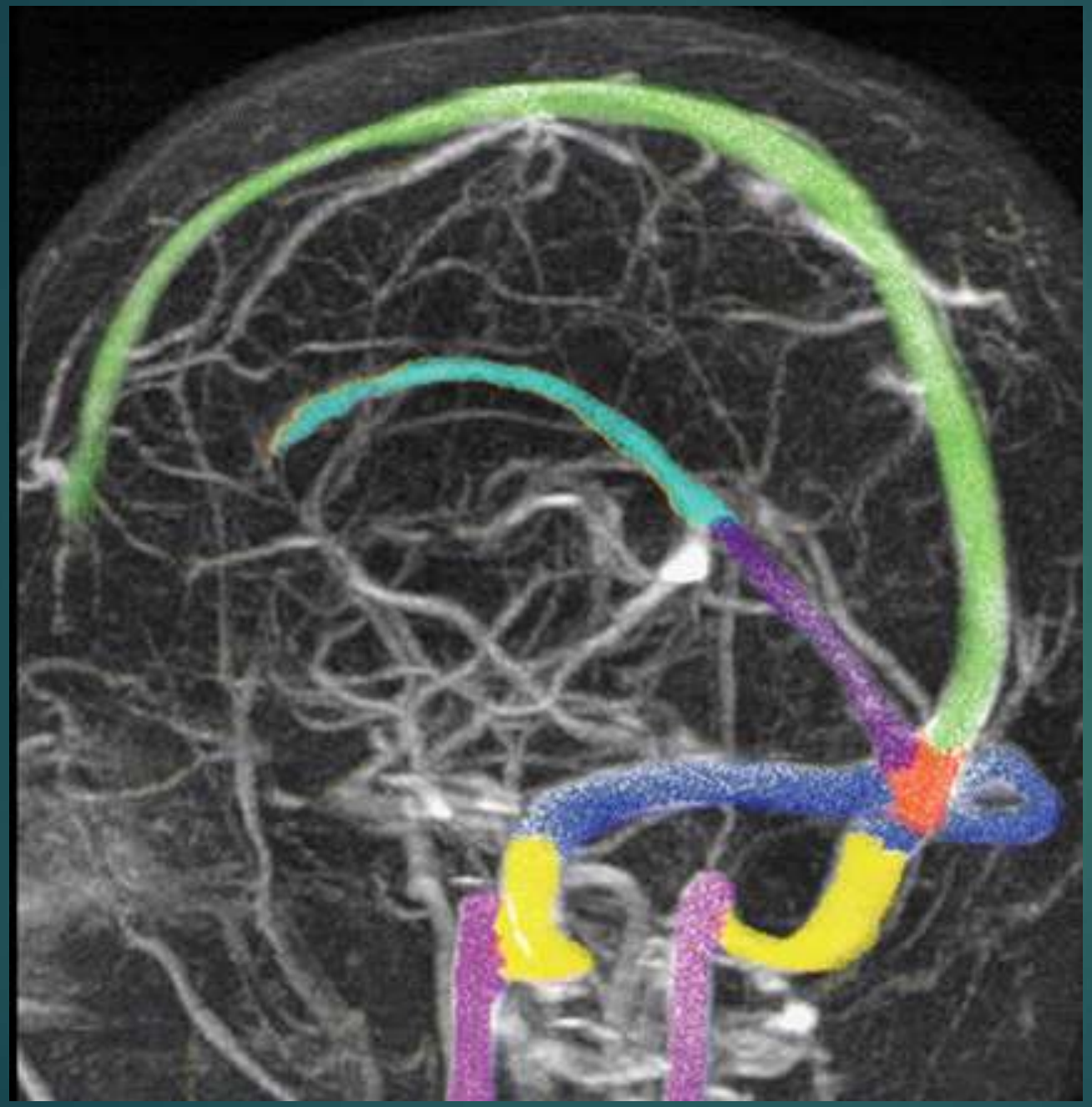


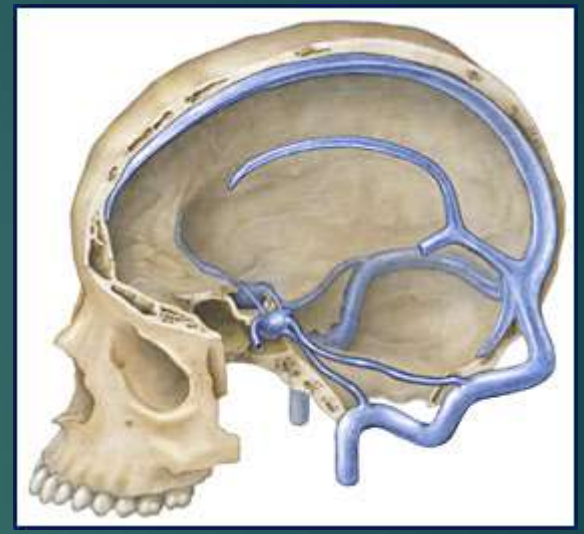
Venous Infarction

- May be bilateral, multifocal (not in a vascular territory)
- May be hemorrhagic
- Superior Sagittal Sinus---Cortical veins: Frontal lobes
- Transverse Sinus---Vein of Labbe: Temporal Lobes
- Straight Sinus---Thalamostriate Veins:
- Thalamus

Multifocal infarction:

- Vasculopathy (Vasculitis, HTN, DM)
- Venous Infarction
- Meningitis





Atrial Fibrillation: electrical storm in your heart

- AF is an electrical arrhythmia of the heart (too fast or slow, or irregularly)
- AF causes the heart to beat chaotically (electrical storm)
- *** Leading cause of stroke
- Increases:
  - risk of blood clots
  - stroke
  - dementia
  - cognitive and functional decline
- Blood thinners (Warfarin, Aspirin) are treatment
- Apple Watch: has FDA approved EKG program that predicts possible stroke: KardiaBand ($199 + $99 year)

Atrial Fibrillation

- AF causes the heart to beat chaotically, increasing the risk of blood clots and, if the condition is left untreated, stroke.
- AF is an important and modifiable cause of ischemic stroke, is associated with an increased risk of covert cerebral infarction.
- AF is an important determinant of cognitive and functional decline, even in the absence of clinical ischemic stroke.

Atrial Fibrillation

- Biggest problem with atrial fibrillation is that if the arrhythmia lasts for a day or two, the ineffective pumping action of the atria (caused by the chaotic electrical activity) can allow blood clots to form within the atria.

- If these blood clots break off and get into the bloodstream, a stroke can result.

- Thus, patients who are in prolonged or chronic atrial fibrillation have a significantly increased risk of stroke.

AF & Dementia

- Convincing evidence of an association between AF and dementia in patients with a history of stroke
- Among people who had survived a stroke, those with atrial fibrillation were 2.4 times more likely to develop dementia.
- Study: n = 37,000 patients.

- The study found AF patients under the age of 70 had a 187% greater risk of all types of dementia compared with the general population.
- But their specific risk of Alzheimer's disease was also up - by 130%.

Brunch, 2009

Hormone Replacement Therapy as risk

- Increased risk of ischemic stroke associated with HRT in postmenopausal women.

- This was confirmed in recent meta-analyses showing a 30% increased risk of stroke, identical for estrogens alone or in combination with progestogen.

Fluency, Memory and risk for stroke

- Those who scored in the bottom 20 percent for verbal fluency are 3.6 times more likely to have a stroke.

- For the memory test, those who scored in the bottom 20 percent were 3.5 times more likely to have a stroke than those in the top 20 percent.

- At age 50, those who scored in the bottom 20 percent of the memory test were 9 times more likely to later have a stroke

Abraham J. Letter, 2010

Effects of stroke

- Acute stages:
  - lateralized effects due to actual stroke
  - secondary diffuse effects due to edema or metabolic changes

Neuropsychological deficits post stroke

- NP deficits are common after stroke and are predicted based on stroke type, vessels affected and location of injury
- Also influenced by underlying CVD variables
- NP deficits post stroke improve over time and tend to recover over time.

Left-Hemisphere strokes

- Speech and language disorders
- Right-sided hemiplegia (paralysis) or hemiparesis (weakness)
- Depression, catastrophic reactions

Right-Hemisphere strokes

- Perceptual and visuospatial distortions
- Left hemiplegia or hemiparesis
- Left-sided inattention/neglect: 45%
- Restricted emotional expression
- Anosognosia (lack of awareness of deficits)

Right-Hemisphere strokes 2

- Inability to interpret implicit messages
- Inability to interpret the speaker’s intent or mental state
- Lack of empathy (RH stroke: higher divorce rates)
- Impaired learning of the topography of new settings

Right Hemisphere strokes 3

- Forgetting where things have been put
- Impaired visual search
- Impaired constructional praxis
- Much higher rate of divorce

Frontal strokes

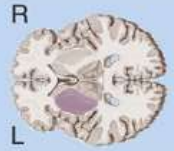
- Often caused by blockage or bleed from anterior communicating artery
- Executive function deficits
- Flat affect
- Decreased motivation and initiation
- Apathy
- Disinhibition

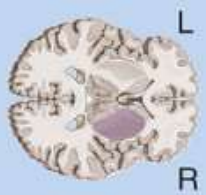
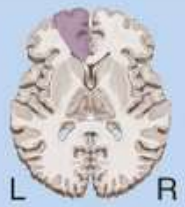
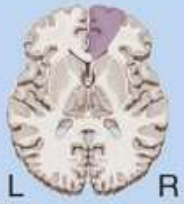
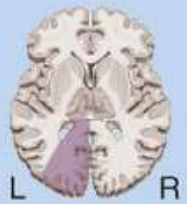
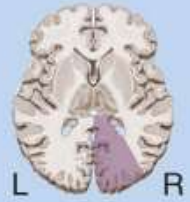
Vascular Lesions and Frontal Lobe Dysfunction

- Large vessel strokes (unilateral damage)
  - LH: speech/language (Broca's), right-sided motor deficits, and depression
  - RH: spatial deficits, left-sided motor deficits, elevated mood
- Ruptured aneurysm of the ACoA
  - Personality changes
- Small Vessel/Microvascular Disease
  - Can occur in F Lobes themselves or in subcortical connections with FLs
  - Variable presentation

NP deficits based
On stroke area

TABLE 10.1 Major Clinical Syndromes of the MCA, ACA, and PCA Territories

LOCATION OF INFARCT	AFFECTED TERRITORY	DEFICITS[a]
Left MCA superior division		Right face and arm weakness of the upper motor neuron type and a nonfluent, or Broca's, aphasia. In some cases there may also be some right face and arm cortical-type sensory loss.
Left MCA inferior division		Fluent, or Wernicke's, aphasia and a right visual field deficit. There may also be some right face and arm cortical-type sensory loss. Motor findings are usually absent, and patients may initially seem confused or crazy but otherwise intact, unless carefully examined. Some mild right-sided weakness may be present, especially at the onset of symptoms.
Left MCA deep territory		Right pure motor hemiparesis of the upper motor neuron type. Larger infarcts may produce "cortical" deficits, such as aphasia as well.
Left MCA stem		Combination of the above, with right hemiplegia, right hemianesthesia, right homonymous hemianopia, and global aphasia. There is often a left gaze preference, especially at the onset, caused by damage to left hemisphere cortical areas important for driving the eyes to the right.
Right MCA superior division		Left face and arm weakness of the upper motor neuron type. Left hemineglect is present to a variable extent. In some cases, there may also be some left face and arm cortical-type sensory loss.
Right MCA inferior division		Profound left hemineglect. Left visual field and somatosensory deficits are often present; however, these may be difficult to test convincingly because of the neglect. Motor neglect with decreased voluntary or spontaneous initiation of movements on the left side can also occur. However, even patients with left motor neglect usually have normal strength on the left side, as evidenced by occasional spontaneous movements or purposeful withdrawal from pain. Some mild, left-sided weakness may be present. There is often a right gaze preference, especially at onset.
Right MCA deep territory		Left pure motor hemiparesis of the upper motor neuron type. Larger infarcts may produce "cortical" deficits, such as left hemineglect as well.

Right MCA deep territory		Left pure motor hemiparesis of the upper motor neuron type. Larger infarcts may produce "cortical" deficits, such as left hemineglect as well.
Right MCA stem		Combination of the above, with left hemiplegia, left hemianesthesia, left homonymous hemianopia, and profound left hemineglect. There is usually a right gaze preference, especially at the onset, caused by damage to right hemisphere cortical areas important for driving the eyes to the left.
Left ACA		Right leg weakness of the upper motor neuron type and right leg cortical-type sensory loss. Grasp reflex, frontal lobe behavioral abnormalities, and transcortical aphasia can also be seen. Larger infarcts may cause right hemiplegia.
Right ACA		Left leg weakness of the upper motor neuron type and left leg cortical-type sensory loss. Grasp reflex, frontal lobe behavioral abnormalities, and left hemineglect can also be seen. Larger infarcts may cause left hemiplegia.
Left PCA		Right homonymous hemianopia. Extension to the splenium of the corpus callosum can cause alexia without agraphia. Larger infarcts, including the thalamus and internal capsule, may cause aphasia, right hemisensory loss, and right hemiparesis.
Right PCA		Left homonymous hemianopia. Larger infarcts including the thalamus and internal capsule may cause left hemisensory loss and left hemiparesis.

Migraine Headaches

- Second most common neurologic disorder
- Headache is 1-sided due to vascular origin
- Severe migraine can be associated with cerebral atrophy and progressive cognitive deterioration
- Migraine headaches are associated with more than twice the likelihood of developing obstructive strokes

Visual Auras

Scintillating Scotoma

Migraine with aura

- Cohort study with over 470,000 person years and a median follow-up of 26 years:
- Men and women with migraine with aura were shown to be at increased risk of mortality from all causes and cardiovascular disease, while those with migraine without aura were not at increased risk.
- Risk of mortality from cardiovascular disease was marginally more increased in men than in women with migraine and aura.
- Migraine with aura is an independent risk factor for cardiovascular mortality in men and women but weaker than major established risk factors, such as cigarette smoking, diabetes, and high blood pressure.

Larus S Gudmundsson, et al., 2010

Vascular Contributions to Cognitive Impairment and Dementia

- A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association **(**Philip B. Gorelick, et al., Stroke, 2011)
- Cerebrovascular disease is associated with dementia
- Vascular contributions to cognitive impairment and dementia are common.

AD and CVD

- Epidemiological studies have correlated recent declines in dementia incidence with improvements in cardiovascular health
- Increasing evidence that AD has a vascular component
- Numerous epidemiological studies have tied cardiovascular risk factors (such as hypertension, diabetes, and obesity) to increased risk of dementia.
- Atherosclerosis is higher in AD brains than in healthy elderly brains, and most cases of AD involve at least some vascular pathology.
- Microinfarcts in the brain increase the risk of dementia and the severity of symptoms
- Major NCD is often “mixed” with both AD and vascular pathology

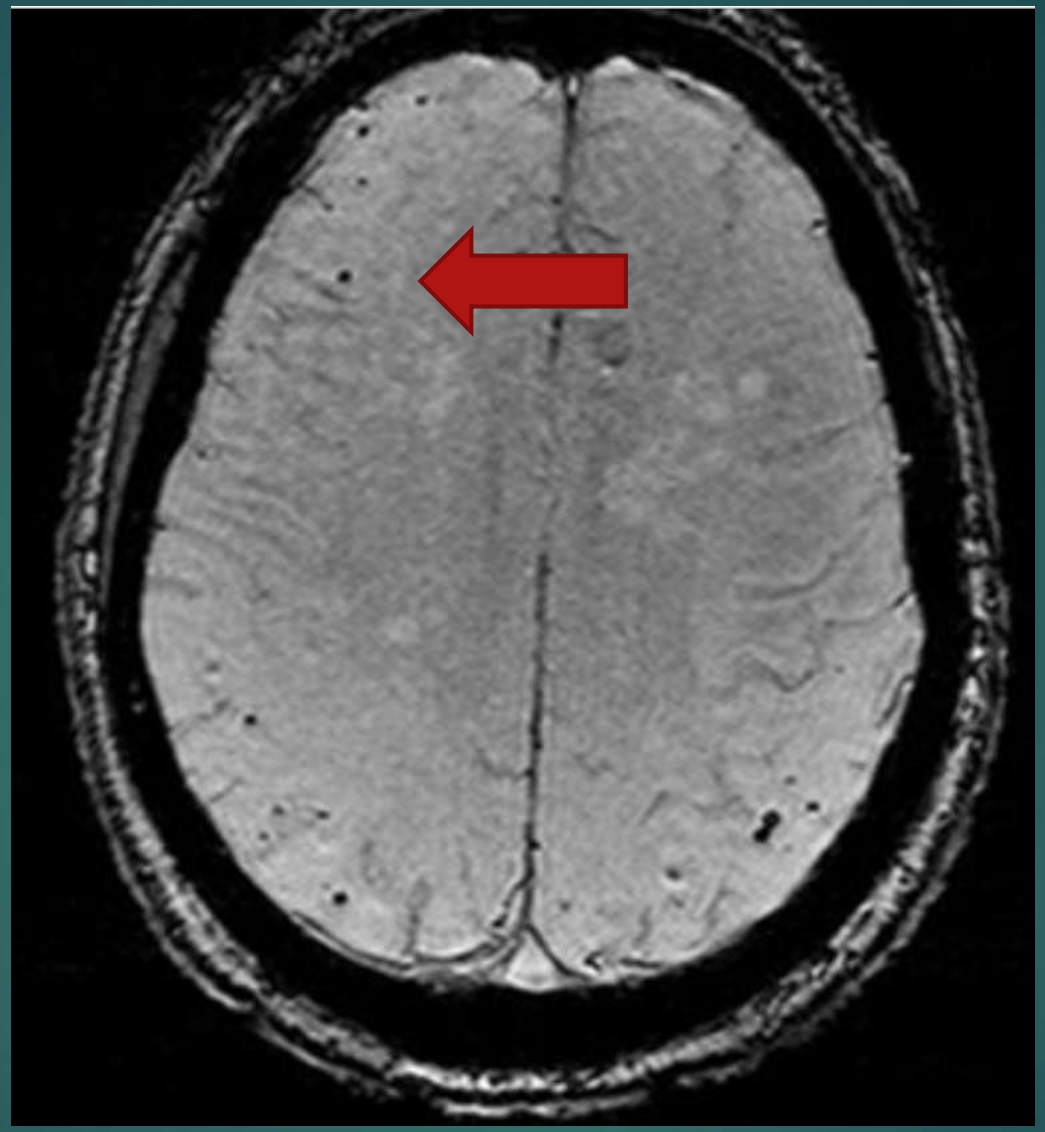
Klohs J, et al., J. Neurosci, 2012

Small vessel damage

- Damage to the walls of the smallest blood vessels of the brain correlates with future cognitive deterioration. Among thousands of volunteers who all started out cognitively normal, those who had cerebral microbleeds declined sooner on cognitive tests and were likelier to later receive a dementia diagnosis than people who didn't have those lesions. This strengthens the notion that cerebrovascular problems contribute to the pathogenesis of Alzheimer's.
- Clusters of hemosiderin-laden macrophages stick around after sopping up the blood and patch up ruptured vessel walls, appearing as small black dots. Microbleeds occur in 11 to nearly 40 percent of older adults and signify that the walls of small blood vessels have weakened
- Microbleeds in the frontal, temporal, parietal, and occipital lobes result from amyloid depositing in blood vessels there; bleeds in the deep white matter seem to stem from hypertension, diabetes, or smoking
- Previous studies suggest that microbleeds are associated with cognitive impairment, measured in lower MMSE scores, but not in those with dementia

Vernooij MW, et al., 2008

Microbleeds

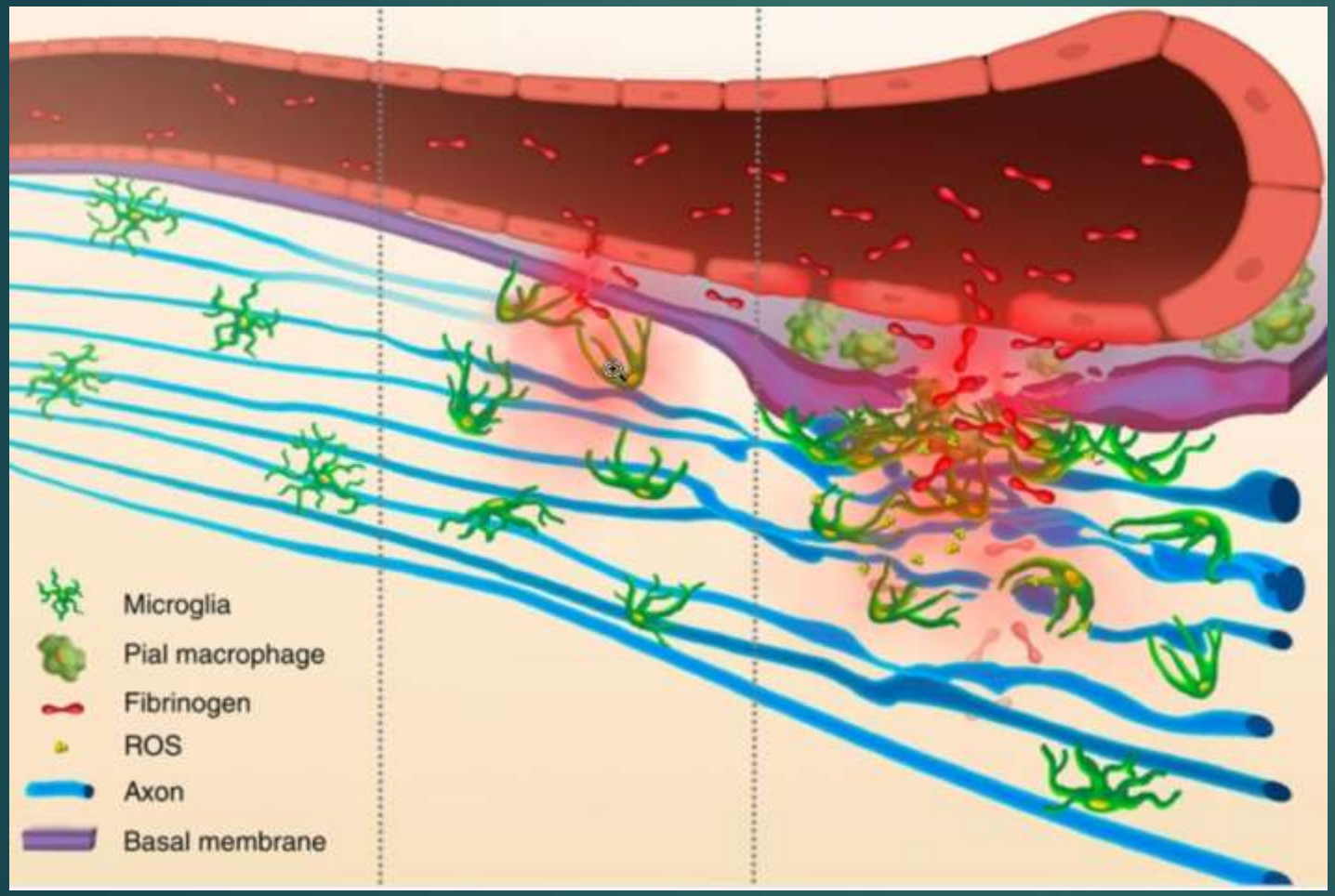


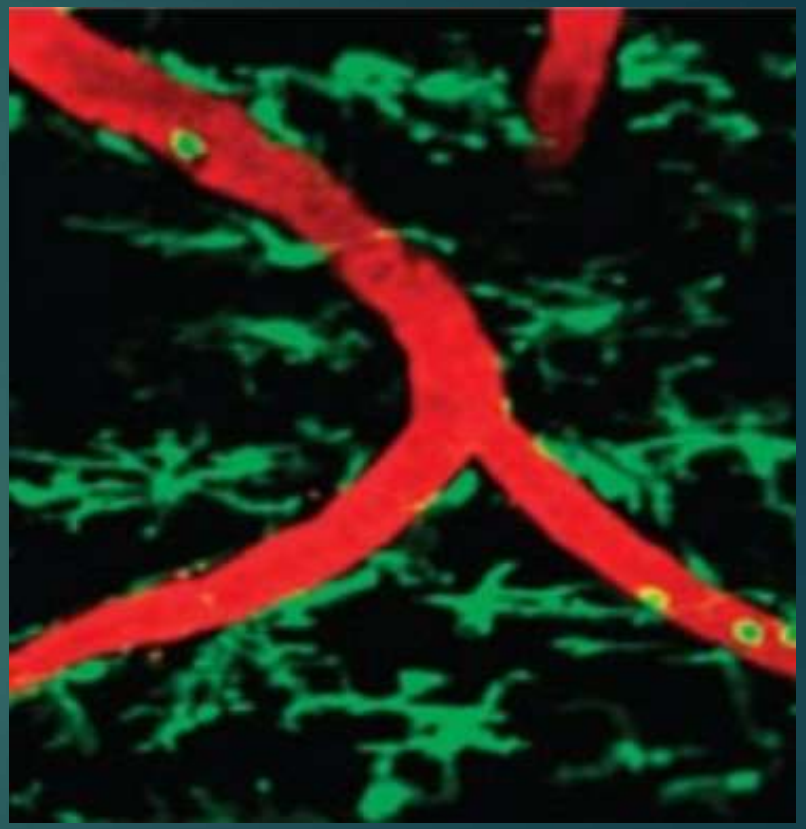
Cerebral microbleeds (black circles) dot the lobar regions of a person without dementia.
[Courtesy of Saloua Akoudad]

Emboli are not good for your brain

- Pts who had occasional small clots/emboli flowing through their cerebral arteries declined nearly twice as fast on several cognitive measures over a two-year period. In about 40 percent of the participants, emboli would occasionally pass through the arteries
- Emboli were equally common in people with AD and in those who had vascular dementia. Although the experiment did not include a control group, in previous work the authors found that emboli occur in only about 15 percent of age-matched, non-demented controls.
- Over the two-year timeframe, people who had emboli deteriorated more than twice as fast on cognitive scales, esp. NPI.
- Emboli are a risk marker for progression of dementia

Fibrinogen mediates perivascular microglial clustering and axonal damage





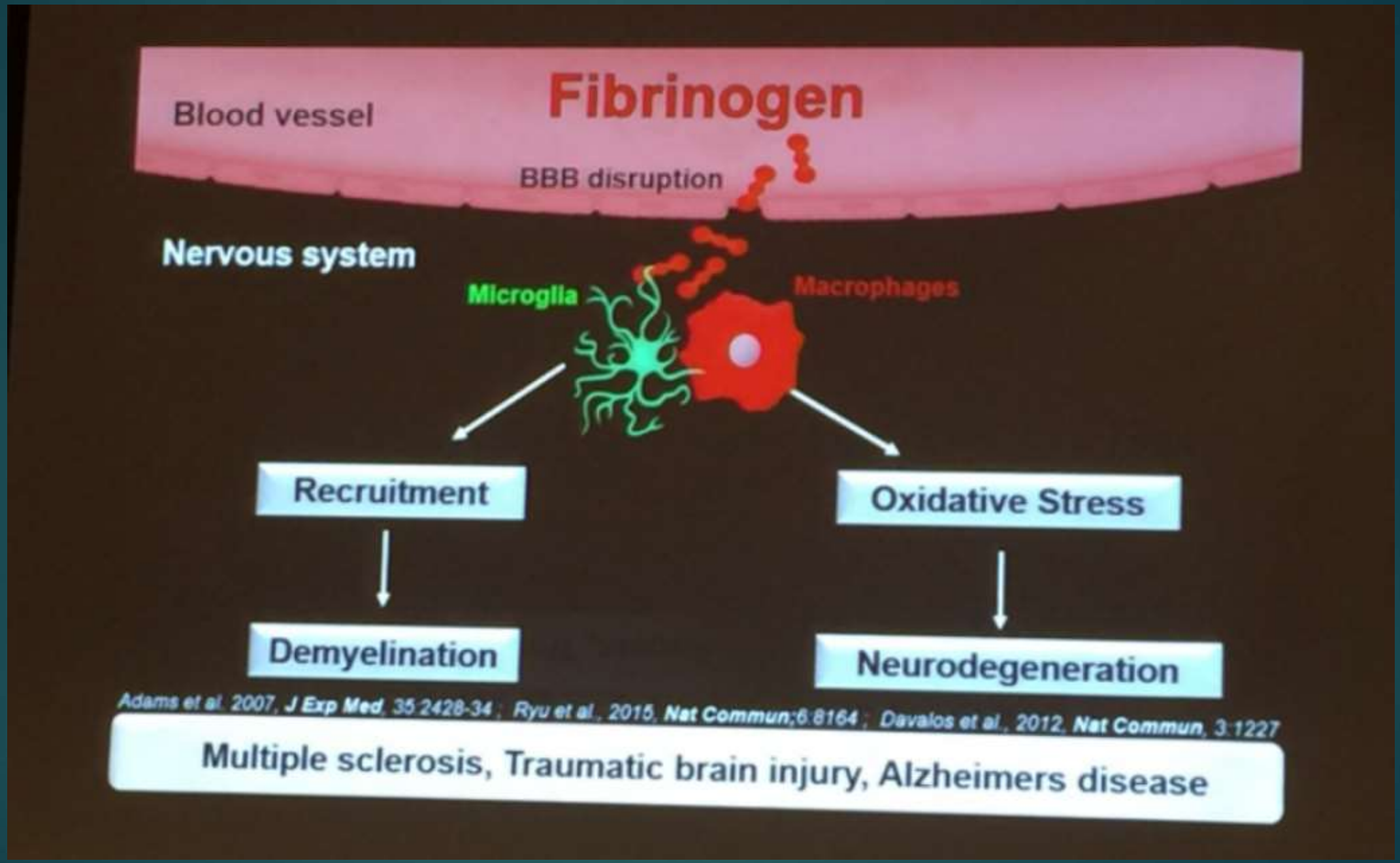
Fibrinogen: response to blood vessel damage

- **Fibrinogen** is a fibrous, non-globular protein involved in the clotting of blood. BBB bleeds involved in MS, Stroke, TBI, Neurodegeneration. The fibrinogen forms a mesh atop the platelet plug that completes a clot.
- Fibrinogen is deposited in the CNS after blood–brain barrier disruption, induces adaptive immune (microglia) responses and peripheral macrophage recruitment into the CNS leading to demyelination.
- Perivascular microglial clustering triggered by fibrinogen leakage upon blood-brain barrier disruption contributes to axonal damage (demyelization) & dendritic loss/spine loss in neuroinflammatory disease. Fibrinogen induces rapid microglial responses toward the vasculature and is required for axonal damage in neuroinflammation.

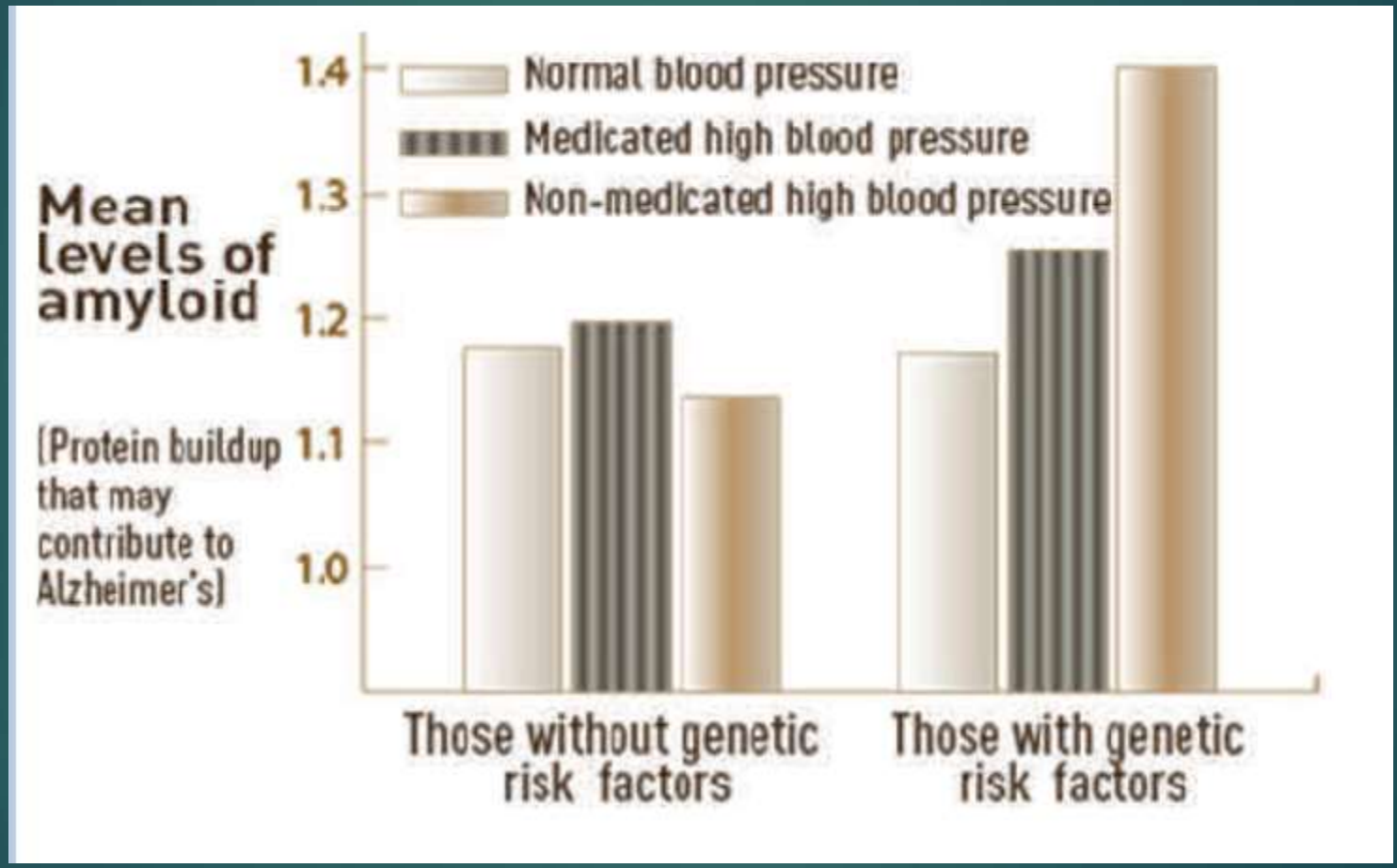
Dimitrios Davalos, et al., 2012; Katerina Akassoglou, 2016

Fibrinogen

- Aβ also binds to fibrinogen.
- Fibrinogen is deposited in brain in AD & correlates with AB plaques in AD.
- APOE4 potentiates deposition of F in amyloid-laden vessels in AD.
- Fibrinogen depletion decreases inflammation & lowers demyelization & cognitive decline.
- It is a CSF & plasma biomarker for MCI & AD.
- 5B8 antibody protects from Fibrinogen effects


Blood vessel
Fibrinogen
BBB disruption
Nervous system
Microglia
Macrophages
Recruitment
Oxidative Stress
Demyelination
Neurodegeneration
Adams et al. 2007, J Exp Med, 35:2428-34 ; Ryu et al., 2015, Nat Commun;6:8164 ; Davalos et al., 2012, Nat Commun, 3:1227
Multiple sclerosis, Traumatic brain injury, Alzheimers disease

Hypertension Increases Beta Amyloid



Bad news: APOE4 & non-medicated hypertension

VD and AD: You often get both

- Almost half of those with clinically probable Alzheimer disease have mixed pathology, most commonly Alzheimer disease and infarcts

- Infarcts are additive with Alzheimer disease pathology in lowering cognitive function and increasing the odds of dementia or clinical Alzheimer disease.

- The neuropathology of cognitive impairment in later life is often a mixture of Alzheimer disease and microvascular brain damage, which may overlap and synergize to heighten the risk of cognitive impairment

Subcortical Ischemic Vascular Dementia

- 2nd most common dementia
- Sudden, stepwise, focal, often motor
- 2 subcortical types:
  - Lacunar
  - Binswanger's (small vessel disease) : periventricular, white matter

Vascular worse than Beta Amyloid

- 2013: Vascular brain injury (high blood pressure & stroke) are greater risk factors for memory & EF impairment in non-demented older people (age 78) than is BA deposition
- Vascular & BA injury do not correlate; vascular injury does not increase BA
- MRI of vascular (infarcts and white matter hyperintensities) & Pet of BA
- Memory and executive function correlated negatively with brain infarcts, especially infarcts in cortical and sub-cortical gray matter; more vascular brain injury the person had, the worse their memory and executive function
- N = 24 – normal, 30 – MCI, 7 – dementia; ave age = 78

B. Reed, et al., JAMA Neurology , 2013

Risk Factors for Vascular Dementia

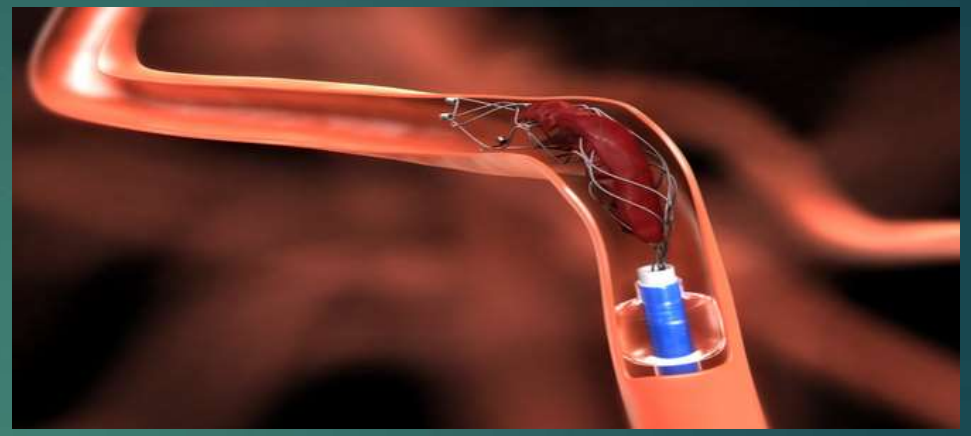
- Atherogenic
  - includes HTN, high cholesterol, diabetes, cigarette smoking
- Cardiovascular disease
- High blood hemoglobin concentration
- Advancing age
- Gender (men < women)
- Race
- Alcohol abuse/dependence, smoking
- Afib

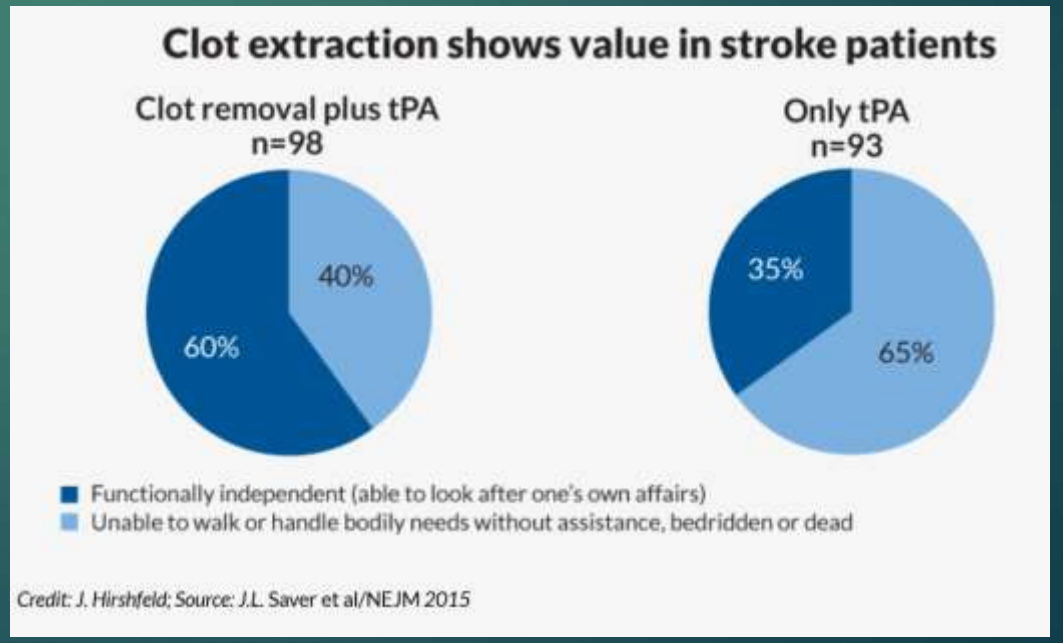
Treatment of ischemic stroke

- The only fibrinolytic agent that has been shown to benefit selected patients with acute ischemic stroke is alteplase.
- While streptokinase may benefit patients with acute myocardial infarction, in patients with acute ischemic stroke, it increases the risk for intracranial hemorrhage and death.
- Fibrinolytics (ie, tPA, tissue plasminogen activator) restore cerebral blood flow in about 30% of patients with acute ischemic stroke; good if within 3 to 4.5 hours after stroke.
- Proper patient selection and protocol adherence is essential because fibrinolytics may also cause symptomatic intracranial hemorrhage.

Solitaire, a clot retrieving device

- A clot retrieval stent can extract 80-90 % of strokes; dramatically better if pt is awake during procedure.
- If within 6 hours of stroke
- tPA can still be used.





Beware…

- Chiropractic neck maneuvers
- Yoga neck and plough positions
- Both can produce strokes

Why stroke prevention is important

- Stroke is the leading cause of disability
  - Only 50-70% regain functional independence
- 3rd leading cause of death (after Heart Disease & Cancer)
- 80% of strokes are preventable

Prevention of CV disease

- Reducing high blood pressure, esp. in mid life.
- Control high cholesterol and abnormal blood sugar
- Smoking cessation
- Increase physical exercise
- Consume a moderate level of alcohol (i.e., up to 2 drinks for men and 1 drink for non-pregnant women) for those who currently consume alcohol
- Maintain a healthy weight

Preventable Cardiovascular Risk Factors:

Stop Strokes & Heart attacks

- Cigarette smoking
- Poor nutrition
- Physical inactivity
- Excessive alcohol use
- Hypertension
- High cholesterol
- Diabetes
- Metabolic Syndrome (Insulin resistance)
- Atherosclerosis→ Impaired cerebral blood flow →Brain infarction (stroke)

7 cardiovascular health metrics

- Presence of a greater number of cardiovascular health metrics is associated with a graded and significantly lower risk of total and CVD mortality
- 1 Not smoking
- 2 being physically active – 3-5x per week
- 3 having normal blood pressure - <120/<80 mm Hg
- 4 blood glucose - less than 100 mg/dL
- 5 total cholesterol levels - level less than 240 mg/dL
- 6 weight - BMI less than 30
- 7 eating a healthy diet: (fruits and vegetables (≥4.5 cups/d), fish (≥two 3.5-oz servings/wk), fiber-rich whole grains (≥three 1-oz–equivalent servings/d), sodium (<1500 mg/d), & sugar-sweetened beverages (≤36 oz/wk))

Usual Suspects:
Conditions that increase risk of stroke

- Ischemic stroke
  - Obesity
  - Diabetes
  - High blood pressure
  - High cholesterol
  - Smoking
  - Sleep apnea

- Hemorrhagic stroke
  - High blood pressure
  - High Alcohol use

Most Strokes Can Be Prevented; 1 in 6 People Will Have a Stroke

- Know your personal risk factors: high blood pressure, diabetes, and high blood cholesterol.
- Take your medications faithfully.
- Be physically active and exercise regularly.
- Avoid obesity by keeping to a healthy diet.
- Limit your alcohol consumption.
- Avoid cigarette smoke. If you smoke, seek help to stop.
- Learn to recognize the warning signs of a stroke.

Cerebral amyloid angiopathy: Microbleeds

- Cerebral amyloid angiopathy, accumulation of amyloid causes degeneration of smooth muscle cells and increases the susceptibility of blood vessels to ruptures and hemorrhages.

- Cerebral microbleeds--small deposits of the iron-storing protein hemosiderin in the brain

- Microbleeds in the frontal lobe were more common among aspirin users than carbasalate calcium users.

M. Vernooij, Arch Neurol. 2009;66[6]:

Recovery

- Majority of functional recovery from stroke occurs over the first few (3-6) months
- Less pronounced recovery occurs over the next 6-12 months
- After 12 months, improved functioning due to compensation and adaptation to deficits
- Marked variability of deficits

Stroke Recovery

- 111 pts tested immediately post Stroke and 6 to 10 months later.
- Improvement seemed to be the rule rather than the exception, with 41 to 83% showing improvement at follow-up
- No evidence of a generalized insidious cognitive deterioration at f/u. 90% of initially unimpaired remained unimpaired.

(Nys et al 2005)

Stroke Recovery 2: Characteristics associated with poor recovery

- Lower NART score
- Older age
- Larger lesion volume
- Greater severity of unilateral neglect
- Diabetes was the only vascular risk factor assoc w/poor recovery in a single domain (i.e., abstract reasoning)
- Loss of consciousness (Ebrahim & Harwood 1999 and others)

Stroke Recovery 3: Characteristics assoc with good recovery

- Higher NART score
- Younger age
- Smaller lesion volume

(the following from Macciocchi et al, 1998)

- No h/o prior Stroke
- Less severe initial neurological deficit
- Stroke involving cortical structures
- Left hemisphere lesions

Possible mechanisms of improvement

- “Hebbian learning mechanism”: involves experience-dependent dendritic sprouting (seen in normal learning)
- Neuronal regeneration
- Brain plasticity: peri-lesional changes and contralateral reorganization
- Cognitive reserve theory: pre-existing ability improves ability to create compensation strategies

The good news

- In a study by Shahar, et al 1995, rates of survival post-Stroke improved significantly between 1980 and 1990.
- Death within 2 years was 40% lower in 1990 than it had been in 1980
- Most of the improvement was attributable to improved odds of surviving ischemic stroke.
- No evidence of improved survival for hemorrhagic stroke.

Neuropsychological Assessment & Functional Outcome

- Neuropsychological factors are more important determinants of functional outcomes after stroke than physical disability

  (Barker-Collo & Feigin 2006)

- Cognitive abilities linked to functional outcome:

  Sustained attention, working memory

  Apraxia

  Pathological emotional reactions

  Language functions (e.g., verbal comprehension)

  Verbal memory (impairment linked to reduced functional independence)

  Verbal abstract reasoning

NINDS Consensus on NP Testing

- Battery:
  - Executive Functioning
    - TMT
  - Attention
  - Visuospatial
    - ROCF
  - Language & lexical retrieval
    - Animal Naming, COWAT, BNT
  - Memory
    - Hopkins or CVLT
  - Speed
    - Coding
  - Neuropsychiatric and Depression (NPI)

Hachinski, et al., 2006

Hachinski Ischemic Score

Abrupt Onset	2
Step-wise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic Complaints	1
Emotional Incontinence	1
History of arterial hypertension	1
History of Stroke	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

Walking Speed and CV death

- Walking speed over 6 m in older people is predictive of cardiovascular mortality, with those in the slowest tertile three times more likely to suffer CV death over five years than those who walked faster.

Stroke Prevention

- Strokes are preventable!!
- Stay at correct weight
- Exercise
- Take your heart medications
  - Antihypertensives
  - Anticholesterol

Keep your heart fit

- 1 - Get moving: People who exercise regularly have a 30 to 40 percent lower risk of heart disease; but prolonged sitting lowers levels of HDL (good) cholesterol, raises artery-clogging triglycerides, and decreases the insulin sensitivity that boosts the risk of type 2 diabetes.

- 2 - Eat more plants: people who eat 8 servings of fruit and vegetables daily--especially dark-green vegetables, orange fruit and vegetables, and citrus fruit--have a 17 percent lower risk of heart disease

Keep your heart fit 2

- Make plant foods and fish the centerpiece of your meals. When you do eat meat or poultry, stick to 3-to-4-ounce portions and choose lean cuts. Replace saturated fat, such as butter, with canola, olive oil, and other unsaturated oils.

- 3 - Relax

- 4 - Drink (a little): raise a low HDL (good) cholesterol level and reduces the risk of death from heart disease by about 25 percent. It may also help prevent type 2 diabetes and ischemic strokes, the kind caused by blood clots.

- 5 - Quit smoking: Smokers are 2 to 4 times more likely to develop heart disease than nonsmokers.

½ glass of wine per day

- Long-term wine consumption is related to cardiovascular mortality and life expectancy independently of moderate alcohol intake

- 1,373 randomly selected men whose cardiovascular health and life expectancy at age 50 were repeatedly monitored between 1960 and 2000. During the 40 years of monitoring, 1,130 of the men died. Over half the deaths were caused by cardiovascular disease.

- Half a glass of wine a day may boost life expectancy by five years in men
- Drinking wine was strongly associated with a lower risk of dying from coronary heart disease, cerebrovascular disease, and death from all causes.

Charles J. Vella, PhD

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