

# Normal and Pathological Aging

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# Brief overview

- Differentiate normal cognitive aging from pathological aging
  - Theories of cognitive aging
  - Cognitive aging by domain
- Differentiate biological functions of aging
  - Amyloid Cascade Hypothesis
  - Neurofibrillary Tangles (NFT)
  - Oxidative stress
  - Apoptosis
- Examine the influences of depression and other psychological issues that occur with age.

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- “Aging makes us neither wise nor foolish nor neurotic.”

- Zarit, S.H. & Zarit, J.M. (2007, p.12)

- Dementia myths (just a few...)
  - Dementia is an inevitable part of aging.
  - Dementia must impair memory.
  - Dementia is a “global” impairment of intellectual functions.

# General Definitions

- “Normal” aging is a result of natural maturational processes whereas “pathological” aging is due to non-normative factors such as disease or trauma to the brain (Reese, Cherry & Copeland, 2000).
- Age brackets
  - Young-old adults: 55-75 y-o
  - Old-old adults: 75-85 y-o
  - Oldest-old adults: 85+ y-o
- Inter-individual and intra-individual variables
  - Age
  - Gender
  - Medical conditions
  - Education

# Cognitive Theories of Aging

- “Classical” Pattern of Aging

- Crystallized intelligence: maintained with little variance over time (Ardila, 2007) and is based on previous learning and general fund of knowledge (Cattell, 1963, Horn & Cattell, 1966, Horn 1985).
- Fluid intelligence: nonverbal or performance tasks that allow the use of current information to solve the new problem (Cattell 1963); steeper and earlier decline.
- Oregon Brain Aging Study (Hickman, Howieson, Same, Sexton & Kaye, 2000)
  - 53 healthy adults: Y-old 65-74; O-old 84-93
  - Cognitive functions are relatively well preserved, except construction and visual perception tasks in O-old
  - Y-old longitudinal decline on vocabulary
  - Practice effects for Y-old.

# Cognitive Theories of Aging

- Processing Speed (Salthouse)
  - A decrease in processing speed may represent the primary factor (or bottleneck) that accounts for many other age related declines
- Reduced Processing Resources
  - The amount of attentional resources available for cognitive processing declines with age (Luo & Craik, 2008).

# Cognitive Theories of Aging

- Frontal-Aging Hypothesis (aka: Inhibitory Deficit)
  - Aging disproportionately affects frontal lobes structure (Pfefferbaum, Adalsteinsson, & Sullivan, 2005).
  - Older adults show working memory deficits caused by less efficient inhibitory mechanisms (Hasher & Zacks, 1988).
  - Executive function deficits as a marker of dementia (Voss & Bullock, 2004; Walts et al., 2004, Baudic et al., 2006).
- Context Processing (Braver et al.)
  - Disturbance in the processing of context that impair cognitive control functions across multiple domains including attention, inhibition and working memory.
  - Two components: activation/updating and maintenance

# “Normal Aging”: Common Complaints

- What are they?
- Diminished ability to remember names
- Diminished ability to find the correct word
- Diminished ability to remember where objects are located
- Diminished ability to concentrate
- Is this “normal”?



# ...the short answer

- YES!
- **Generally** (modified from Mendez, M.E. & Cummings, J.L., 2003)
  - General slowing of neuronal and sensory processing.
  - Decreased perception and increased spatial segmentation
  - Decreased complex, divided, and sustained attention
  - Decreased primary and working memory
  - Decreased retrieval of stored memory
  - Attenuation of certain personality traits

# Cognitive Aging by Domain

- No uniform neuropsychological profile of normal aging.
  - However, domains most susceptible to age-related decline: memory, processing speed, and executive functions.
- Attention
  - Aging: less efficient, decreased ability to concentrate, some difficulty with divided attention and discriminating relevant and irrelevant information
  - Dementia:
    - Early and/or mild AD: same as normal aging
    - FTD and Vascular Dementia - complex attentional deficits

# Cognitive Aging by Domain

- Language

- Aging: relatively spared; increasing narrative style, decrease active naming
- Dementia: empty, overall impoverished
  - Aphasia
  - Poor word list generation
  - Initial word finding leads to anomia

- Visuospatial/Construction

- Aging: relatively intact, decline due to attention or processing speed constraints
- Dementia: inability to make drawings or constructions or to orient themselves to surroundings
- Processing speed: by age 60 RT decreased 20%; by age 80 RT decreased 40-60%

# Cognitive Aging by Domain: Executive Functions

- Aging:
  - Intact:
    - Set shifting for visual information
    - Some abstract verbal reasoning
    - Some cognitive flexibility
  - Some Decline in
    - Some adaptation to new situations
    - Some set shifting for verbal information
    - Divided attention
    - Complex problem solving
    - Inhibition

# Crawford & Channon studies (1999, 2000)

- Examined problems solving abilities using real life videotaped situations and standard neuropsychological tests
- 30 OA (age 60-80) v 30 YA (age 19-37)
- Results:
  - OA = fewer number of solutions but higher quality
  - OA < YA on most neuropsych tests and speed based measures

# Cognitive Aging by Domain: Executive Functions

- AD:
  - Early stages insight into deficits
  - Progression: loss of insight, judgment, motivation, initiation of activities
- FTD
  - “dysexecutive syndrome”
    - Large deficits in insight, abstraction, planning, problem solving
    - Lack of judgment decreased motivation

# Executive Functions: Bisiacchi, Borella, Bergamaschi, Carretti & Modini (2008)

- Examine:

- Whether memory and executive functions decline at the same time or to the same extent in healthy aging?
- Do a-MCI patients have only memory deficits or also exec fx deficits?
- What are crucial features that differentiate a-MCI from both normal elderly and AD patients?

- Study I

- YO>OO: Overlapping Figures and Puzzle Test

- Study II:

- Visual Pattern Test: a-MCI and AD worse than control ( $p < 0.5$ ,  $d = 0.82$ ;  $p < 0.001$ ,  $d = 1.49$ )
- Exec fx tests: Old-old and a-MCI significantly better than AD
- Memory and Exec fx tests: a-MCI performed as well as controls and both performed significantly better than AD

# Cognitive Aging by Domain: Memory

- Frequent “normal” complaints:
  - Forget names, dates, spatial location (I.e. where did I put my keys?)
- Abnormal complaints:
  - Forget names of close friends or relatives
  - Confusion in space and time
  - Agnosia and apraxia
- Memory: not a unitary process:
  - Implicit Memory (procedural and sensory)
  - Working Memory
  - Declarative/Explicit (semantic and episodic)



# Areas that show substantial age related decline

- Encoding and Retrieval
  - Free recall v recognition
  - Visual encoding v auditory
- Source and Context
  - Age differences in context memory is reliably greater than in content memory (Spencer & Raz, 1995).
  - Problems in associative links.
  - OA do better with sources/context that are salient, distinctive and conceptual versus then they are similar and perceptual (Luo & Craik 2008 citing Ferguson et al).

# Memory

- False Memory
  - Driven by high level of familiarity in combination with a lack of recognition to counteract them.
- Prospective Memory
  - Morning is the optimal time of day for OA whose performance in the morning can equal or exceed those of YA whose optimal time is usually later in the day (Luo & Craik 2008).

# Cognitive Aging by Domain: Memory

- For healthy older adults:
  - create supportive conditions to minimize the demand for controlled processes (i.e. environmental change/cues)
  - train efficiency in strategic and controlled processes (i.e. training recollection/attention/cues/mnemonic/loci)
- Dementia patients:
  - AD
    - No significant difference on recall and recognition tasks;
    - Lack of active learning strategies
    - Poor performance on semantic memory (category fluency)
  - Vascular
    - Poorer retrieval and procedural memory than AD
  - FTD
    - Not classically amnesic

# Rogers, Kang & Miller (2007)

| Domain                         | AAMI  | MCI  | AD   |
|--------------------------------|---|--|--|
| Age (years)                    | >50   | >50  | Typically >65  |
| Subjective memory complaint    | Yes   | Yes  | Yes (early stages)                                     |
| Memory test scores             | $\geq 1$ SD below the mean for young adults | $\geq 1.5$ SD below the mean for age-matched peers | Generally $\geq 2$ SD below mean for age-matched peers |
| Non-memory test scores         | Intact                                      | May or may not be impaired                         | Impairment in at least 1 non-memory domain             |
| ADL                            | Intact                                      | Intact   | Impaired   |
| Global IQ and cognitive skills | WNL (MMSE>24)                               | WNL (MMSE $\geq$ 24)                               | IQ decline from pre-morbid level (MMSE <24)            |

# MCI, AD and Normal Aging

Grundman, M., Petersen, R.C., Ferris, S.H., Thomas, R.G., Aisen, P.S.,  
Benett, D.A., et.al, (2004)

- Objective: to define baseline characteristics of patients with MCI
- 769 patients with MCI, 107 cognitively normal elderly controls, 122 patients with very mild AD, and 183 patients with mild AD
- Results:
  - More likely to carry APOE4 allele than controls, less likely than AD
  - MCI had mean ADAS-Cog scores intermediate between Controls and AD CDR 0.5 (on ave MCI performed less than 1 SD below normal on non-memory cognitive measures)
  - Hippocampal volumes approximately 1.0 SD smaller than controls and 0.9 SD larger than patients with AD

# Dementia - Temporal Aspect

(Modified from Mendez & Cummings p 52)

- 4 aspects
- Temporal
- Cognitive
- Behavioral
- Neurologic

|                        | Subacute onset<br>(< month)              | Gradual onset   |
|------------------------|--|---|
| Slowly progressing     |  | AD, FTD, DLB,<br>Normal pressure<br>hydrocephalus,<br>Schizophrenia-<br>related |
| Rapidly<br>Progressive | Creutzfeldt-Jakob                        |   |
| Static                 | Depression                               |   |
| Stair-Step             | Vascular Dementia                        | Vascular Dementia   |
| Fluctuating            | Metabolic<br>Disorders,<br>Demyelination | Metabolic<br>disorders,<br>Demyelination  |

# Aspects of Dementia: DLB v AD

## ● Cognitive

- DLB < AD: attention, letter fluency, visual perceptual organization, visual construction (Hansen et al 1990; Ferman et al 1999, 2002, 2007); DRS construction (Salmon et al 1996).
- AD < DLB: DRS memory (Salmon et al 1996), memory and object naming (Ferman et al 1999, 2002).

## ● Behavioral

- DLB: non-specific tremors, visual hallucinations, wandering

## ● Neurologic

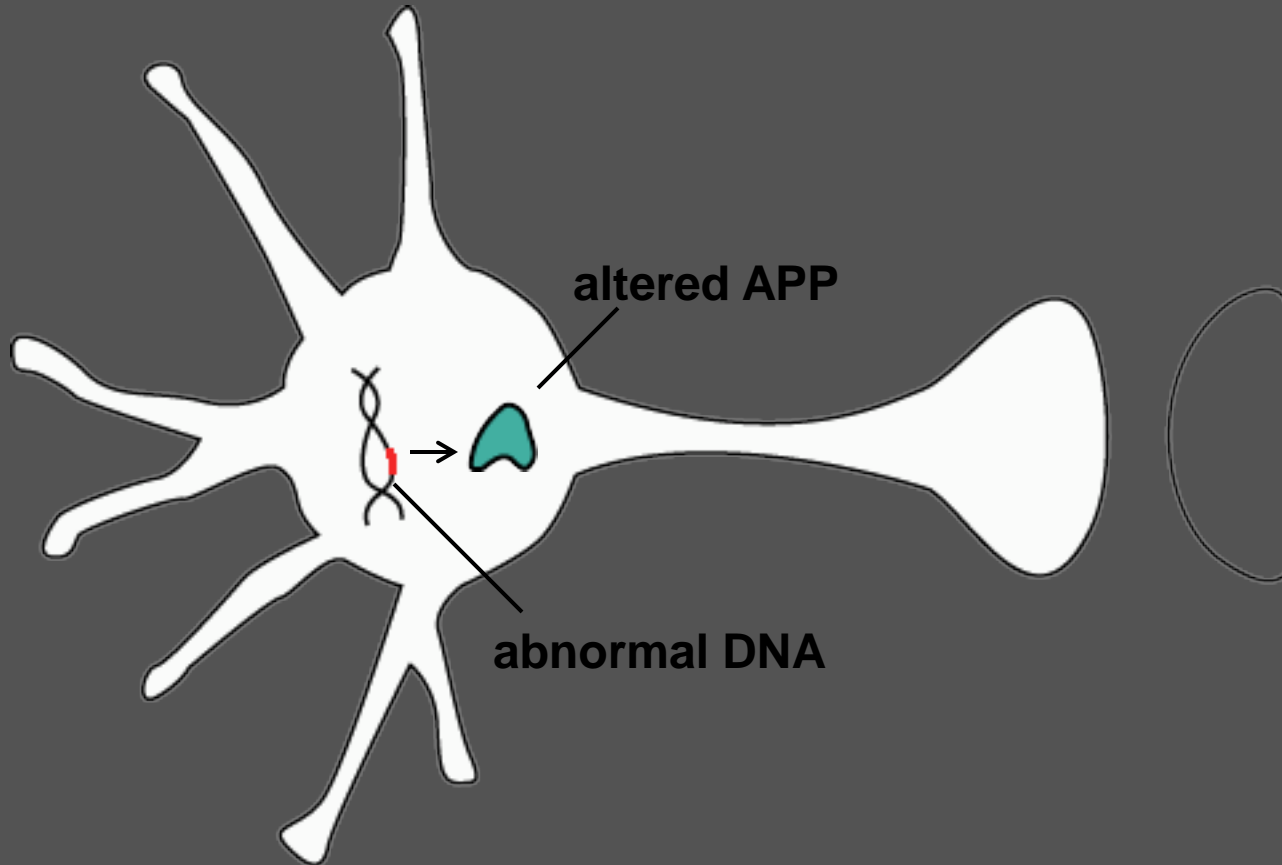
- Neuritic plaques/frequency of NFT
- DLB: presence of Lewy Bodies; substantia nigra
- AD: hippocampal atrophy; neuronal loss also in medial temporal and frontal cortices

# Biology of Aging

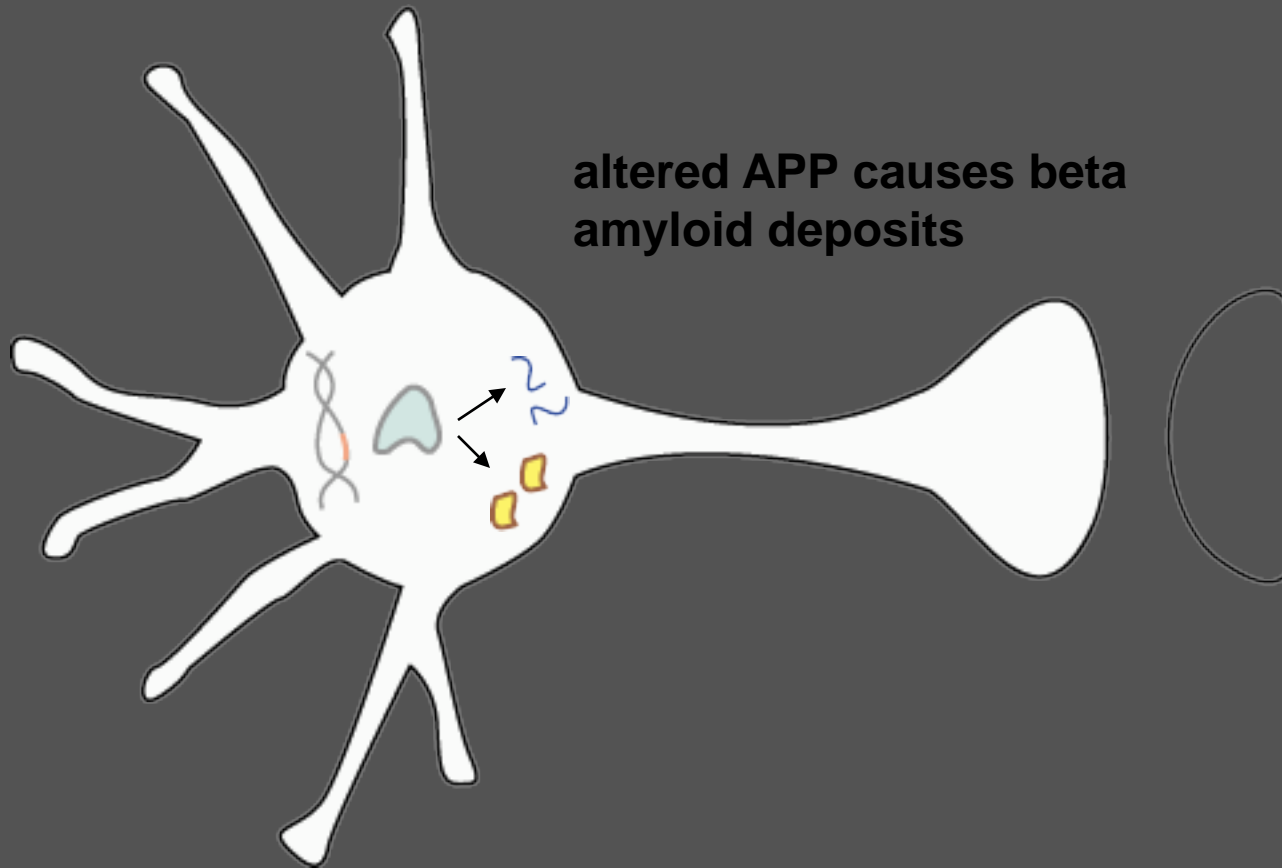
- Structural changes with age
  - Brain weight declines by approx 2-3% per decade after age 50 and continues to accelerate with a 10% decrease in weight by age 80
  - Minimal tissue loss in the parietal and occipital lobes, 12% loss in the frontal lobes, 9% loss in the temporal lobe
  - Cortical sulci and ventricles increase 20% per decade
  - Reduction in density of synapses
  - Senile plaques and neurofibrillary tangles (NFT) gradually accumulate plus neuronal loss
  - Deterioration in white matter integrity
- Other changes
  - Decrease in cerebral metabolism of oxygen and blood flow particularly in pre-frontal and temporal areas
  - changes in the cholinergic and dopaminergic transmitter systems



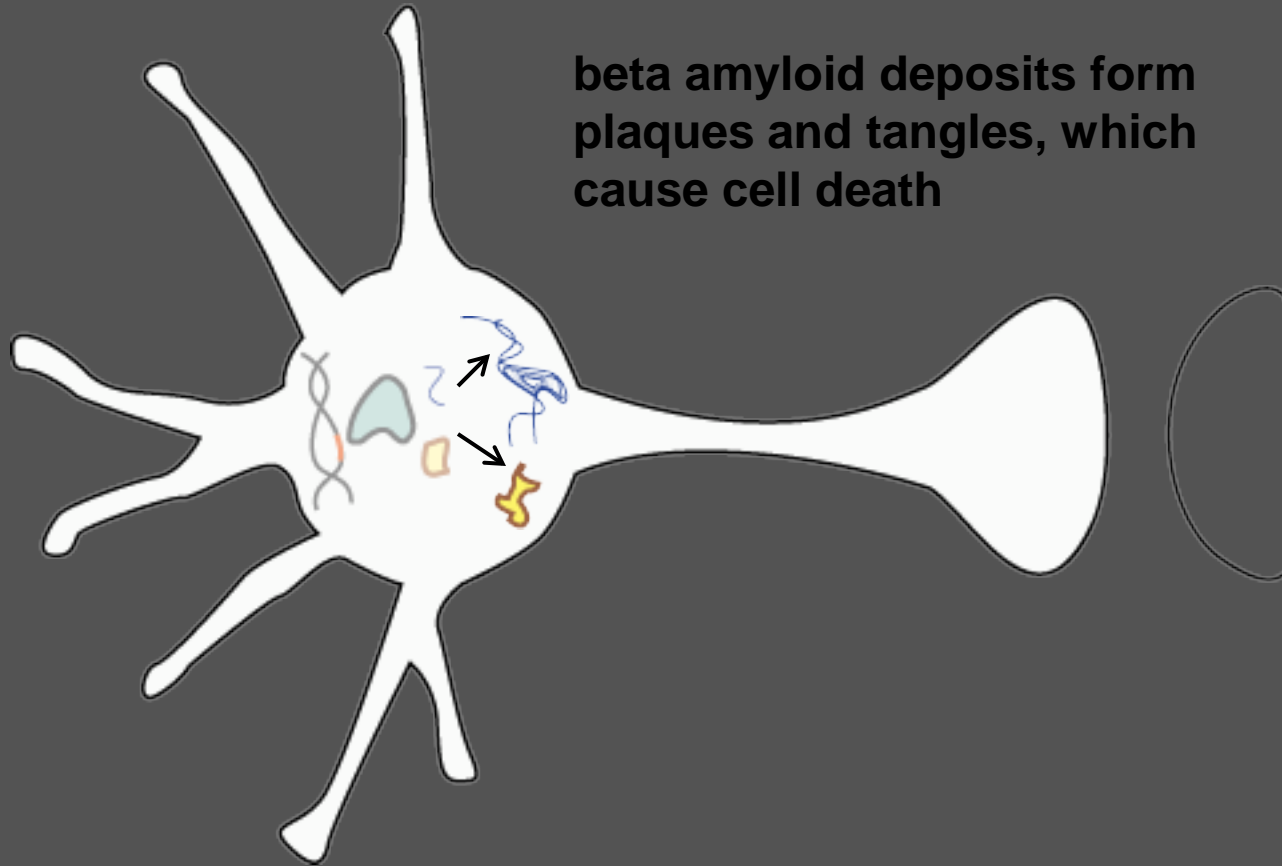
# AMYLOID CASCADE HYPOTHESIS

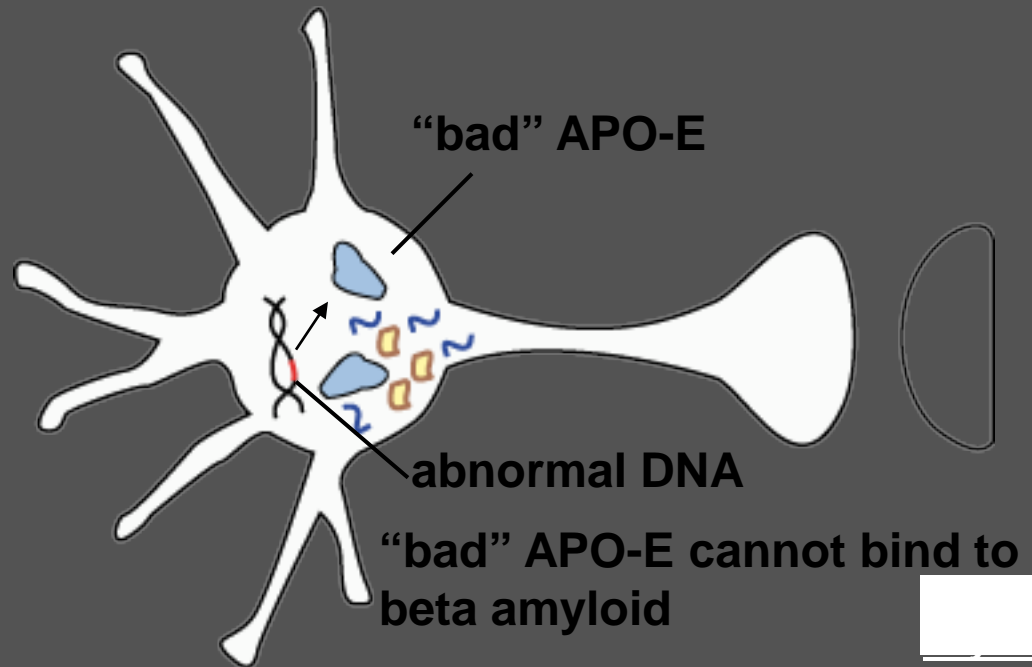
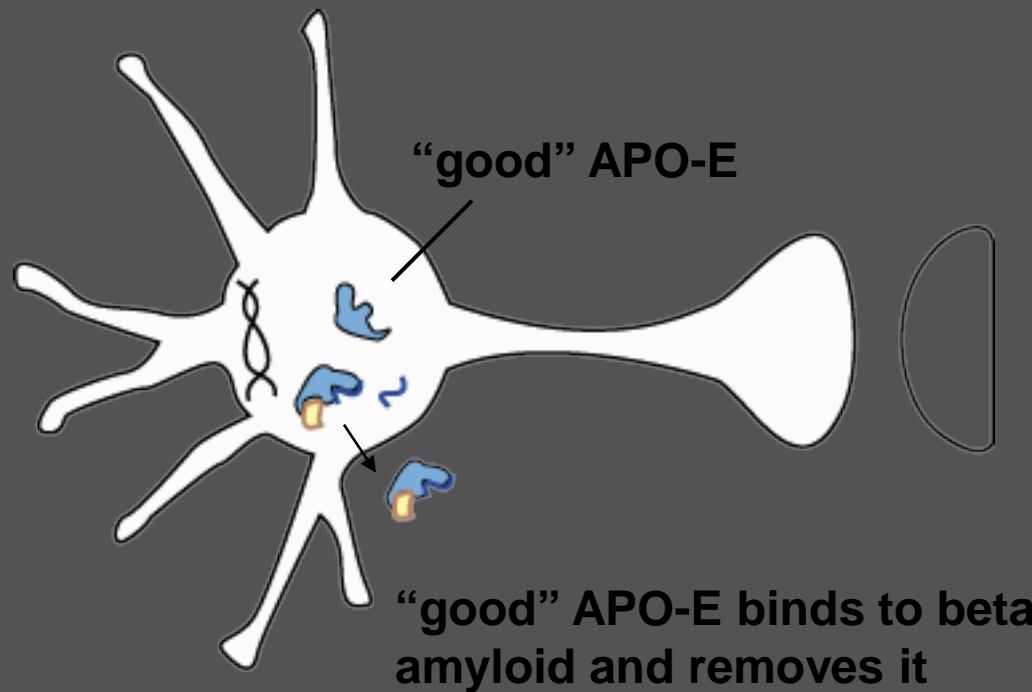


# AMYLOID CASCADE HYPOTHESIS



# AMYLOID CASCADE HYPOTHESIS



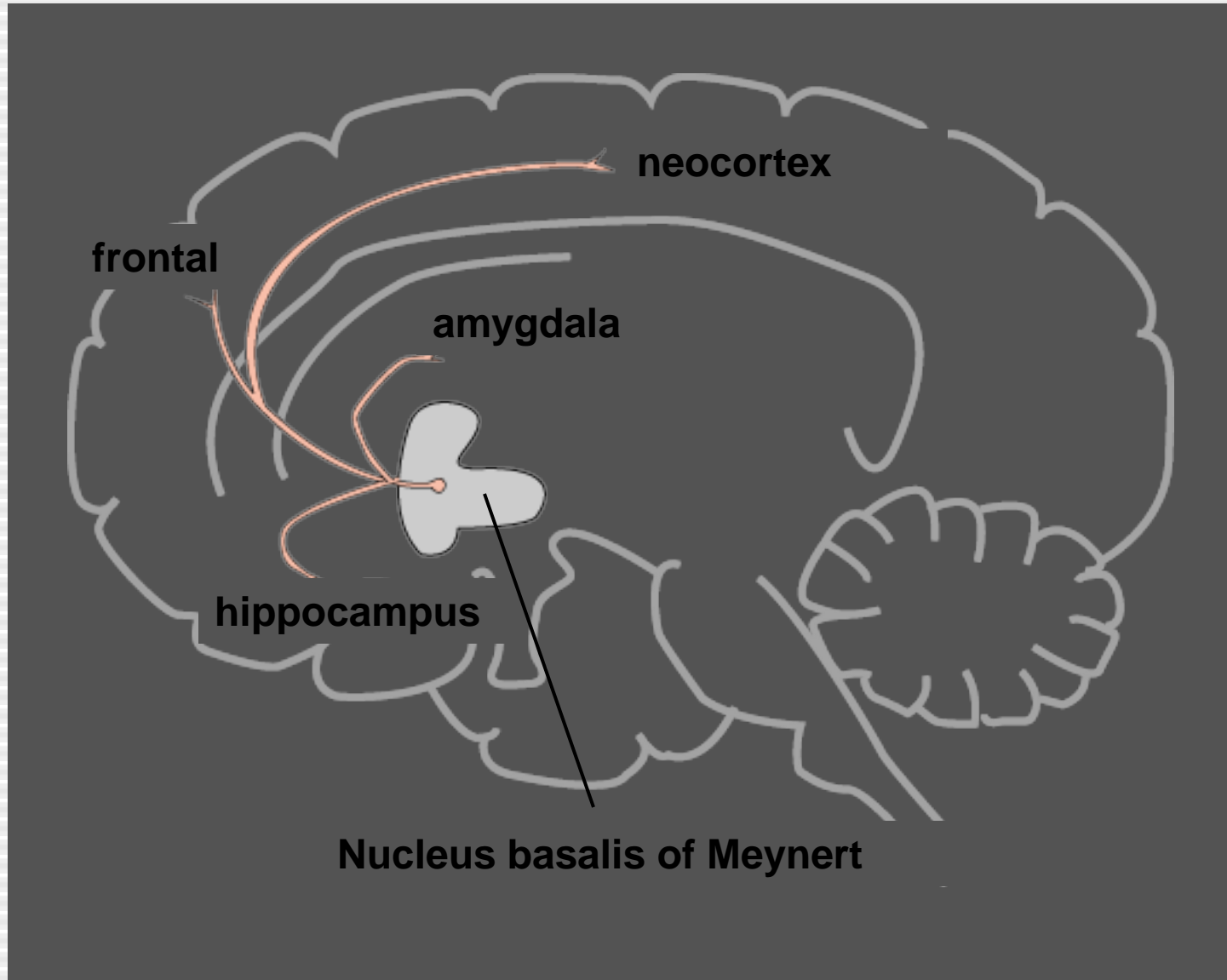


Stahl, S. (2008)  
Essentials of  
Psychopharmacology

12-21  
12-22

*Essential  
Psychopharmacology (2000)*

# Acetylcholine Pathways



# Oxidative Stress

- A condition in which the production of free radicals, and the damage they cause, exceed the ability to scavenge these free radicals or repair their damage (Butterfield, Howard & LaFontaine 2001).
- Free oxygen radicals or reactive oxygen species (ROS) damage mitochondria, DNA, proteins, lipids.
- Natural anti-oxidants superoxide dismutase (SOD) and catalase reduce the oxidative stress
- In AD: the brain is under pronounced oxidative stress and beta amyloid appears to be a source.

# Apoptosis - Programmed Cell Death

- Orchestrated form of cell death to eliminate unneeded, damaged or senescent cells.
- Apoptosis involves both morphological and biochemical features which create a complex cascade effect culminating in cell death.
- In AD: little overt evidence, but beta amyloid is the leading candidate for activation of the apoptotic mechanisms.

# Disorders of Apoptosis and Human Diseases

- Diseases Associated with the Inhibition of Apoptosis

- Malignancies
- Systemic lupus eruthematoses
- Autoimmune lymphoproliferative disorder
- Viral infections
- Chronic inflammation

- Diseases Associated with Increased Apoptosis

- Myelodysplastic syndromes
- Neurodegenerative disorders
- Bacterial infection
- Insulin-dependent diabetes mellitus
- AIDS
- Alcohol liver disease
- Tissue ischemic injury

Joaquin & Gollapudi (2001)



# Effects of Psychological Disorders

- Depression
  - Prevalence of clinical depression among older adults is 1-5% which is lower than the rates for adults in early and middle adulthood (Zarit & Zarit, 2007).
  - “clinically significant” symptoms in OA = 10-25%
  - MDD in older hospital patients average 12% (Koenig & Boeing, 1992).
  - Depression is co-morbid:
    - 33% with diabetes
    - 42% with cancer
    - 45% recently suffering a heart attack

# Depression in OA differs...

- Increased psychotic symptoms/delusions
- Increased hypochondriacal symptoms
- Increased executive functioning deficits
- No report of depressed feelings
  - Report decrease in positive feelings
  - Show a decrease in positive emotions
- Primary behavioral characteristics:
  - Diminished self-care
  - Irritability
  - Psychomotor retardation

# Risk Factors for Depression in Older Adults

- Female, unmarried, or widowed;
- Experiencing stressful life events;
- Lacking social support;
- Having a chronic illness;
- Living in a nursing home;
- Being a caregiver;
- Being an ethnic minority.

|                          | Depression  | AD   |
|--------------------------|---|--|
| Duration/course          | At least 2 weeks, sometimes months, diurnal                                     | Months to years  |
| Mood/affect              | Depressed mood/anhedonia  | Apathy, Disinterested, detached  |
| Psychomotor speed        | Mental and physical slowing   | Normal to mildly slowed  |
| Attention                | Borderline selective attn, difficulty with complex attn                         | Normal to mildly abnormal until late   |
| Memory                   | Mild impairment, memory retrieval difficulty                                    | Abnormal, amnesic pattern in most cases  |
| Speech/language          | Decreased amounts of speech   | Anomic aphasia, empty of sparse content  |
| Other cognition/behavior | Difficulty with effortful tasks; indecisive, delusions and other psychiatric sx | Multiple cognitive domains; psychiatric symptoms may be present but are less prominent |
| Physical symptoms        | Lack of energy, sleep, appetite disturbance                                     | Usually none until middle/late stages  |

# Psychological Disorders

- Emotional wellbeing
- Bipolar
  - OA: less euphoria, more dysphoric mood; increased cognitive problems than YA (Koeing & Blazer, 2004)
- Anxiety
  - YA>OA
  - Physical changes are particularly common among older adults and include dry mouth, sweating, dizziness, headaches, chest pain, insomnia, etc.
- Psychopharmacological interventions must be used carefully in older adults because they can cause decreased mental functioning and older adults required lower dosages

# Content Specific Delusions: Capgras Syndrome

- The belief that well-known persons, such as family members have identical doubles or imposters (Malloy, Cimino, Westlake, 1992).
- Neuropsych testing: spatial, executive and nonverbal memory problems consistent with right frontotemporal localization on neuroimaging studies

# Summary

Rogers, Kang, & Miller (2007)

- Cognitive profile normal aging

- Declines generally emerge in working memory, declarative memory and prospective memory.
- Remote memory, semantic memory and procedural memory remain relatively intact.
- Some forms of abstract verbal reasoning and nonverbal problem-solving may remain relatively preserved, but divided attention, inhibition and set shifting seem adversely affected by age (supports frontal aging hypothesis).
- Crystallized abilities may continue to improve into late adulthood. Fluid abilities appear to peak in mid-20's and then gradually decline.

# Summary

Rogers, Kang, & Miller (2007)

## ● Mediating factors

- Neuropsychological performance becomes less stable with advanced age.
- Women have more variable processing speed and better verbal memory, men show less rapid decline in speed and reasoning.
- Medical conditions increase risk for aging related cognitive deficits, including APOE4.
- Advanced education may have a protective effect against cognitive decline.

## ● Corresponding biological factors

- Cerebral atrophy, ventricular enlargement and hippocampal atrophy are evident early in the aging process.



# Summary

Rogers, Kang, & Miller (2007)

- Additional neuropsychological profiles associated with aging
  - AAMI: subjective memory complaint, intact neuropsychological performance compared to same age peers, but below that of YA.
  - MCI: subjective memory complaint, intact ADLs, normal intellectual and cognitive fx, abnormal memory compared to same aged peers (1.5 SD)
  - Dementia: cognitive impairment in multiple domains compared to same age peers, impaired social or occupational fx from previous level of fx.

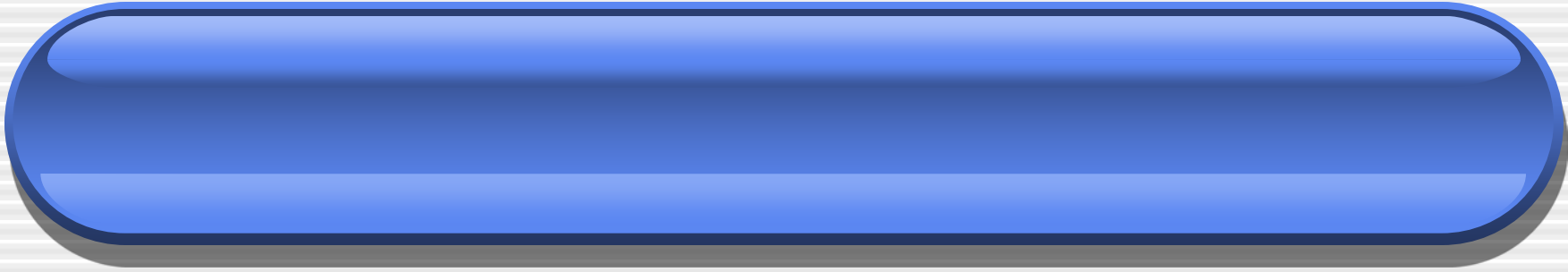
# Conclusions

- Remember, many people with MCI do not progress to AD.
- Recognition of memory complaints should prompt the individual to evaluate their support systems in preparation for deterioration in the future.

# Symptoms To Watch

modified from UCSF Memory and Aging Center Website

- Getting lost in familiar places
- Repetitive questioning
- Odd or inappropriate behaviors
- Forgetfulness for recent events
- Repeated falls or loss of balance
- Decline in planning and organization
- Changes in eating/diet
- Change in hygiene
- Increased apathy
- Changes in language ability including comprehension

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- Thank you for this opportunity!
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