Memory disorders and cortical changes with dysfunction

Geoffrey K Aguirre, MD, PhD

Penn

These slides were created by GK Aguirre and may be distributed and used for instructional purposes freely.

For updated versions, please visit the website:

http://cfn.upenn.edu/aguirre

GK Aguirre 2013

Topics

- Normal memory systems
- Amnesias
- Normal aging
- Dementias (MCI, AD, FTD, vascular, DLB, subcortical)
- Cognitive and behavioral effects of drugs

Appendix

- Dysmnesias (“borderline syndromes”)
- Reversible dementias (B_{12} deficiency, NPH, syphilis)
- Drug effects

GK Aguirre 2013

Memory systems - duration

Short-term memory -

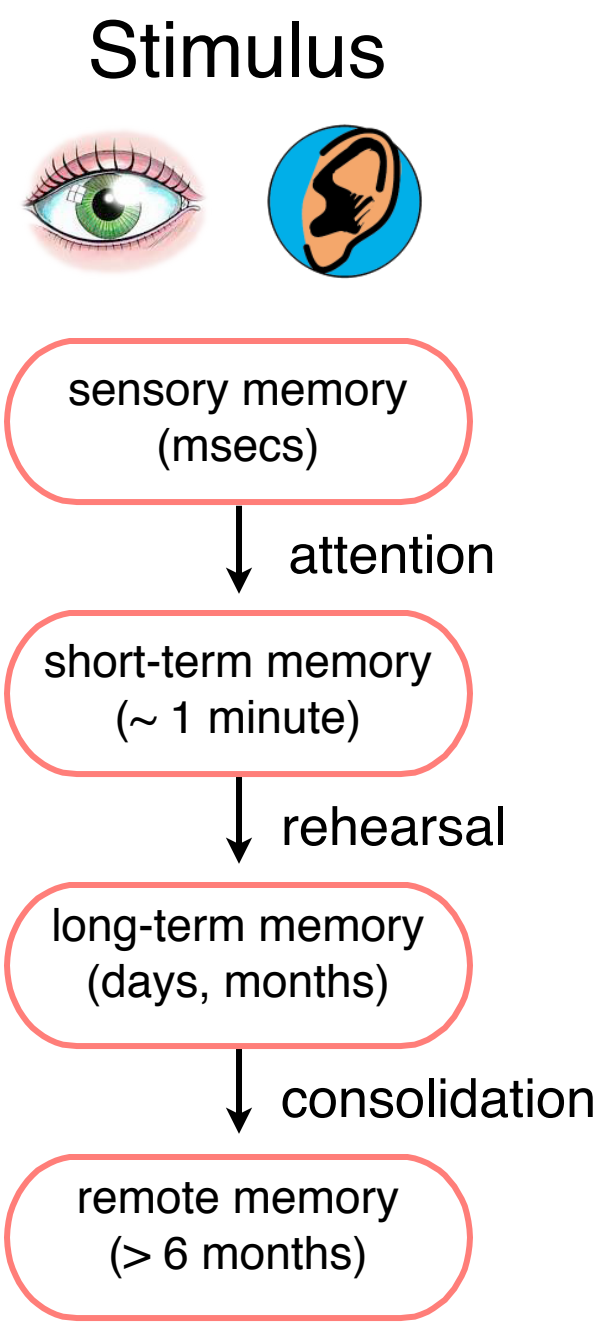
- aka working and immediate memory
- ability to hold information across an undistracted delay
- pre-frontal cortex

Long-term memory (new memories) -

- memory of thing not lost by distraction
- hippocampus, basal forebrain, Papez circuit

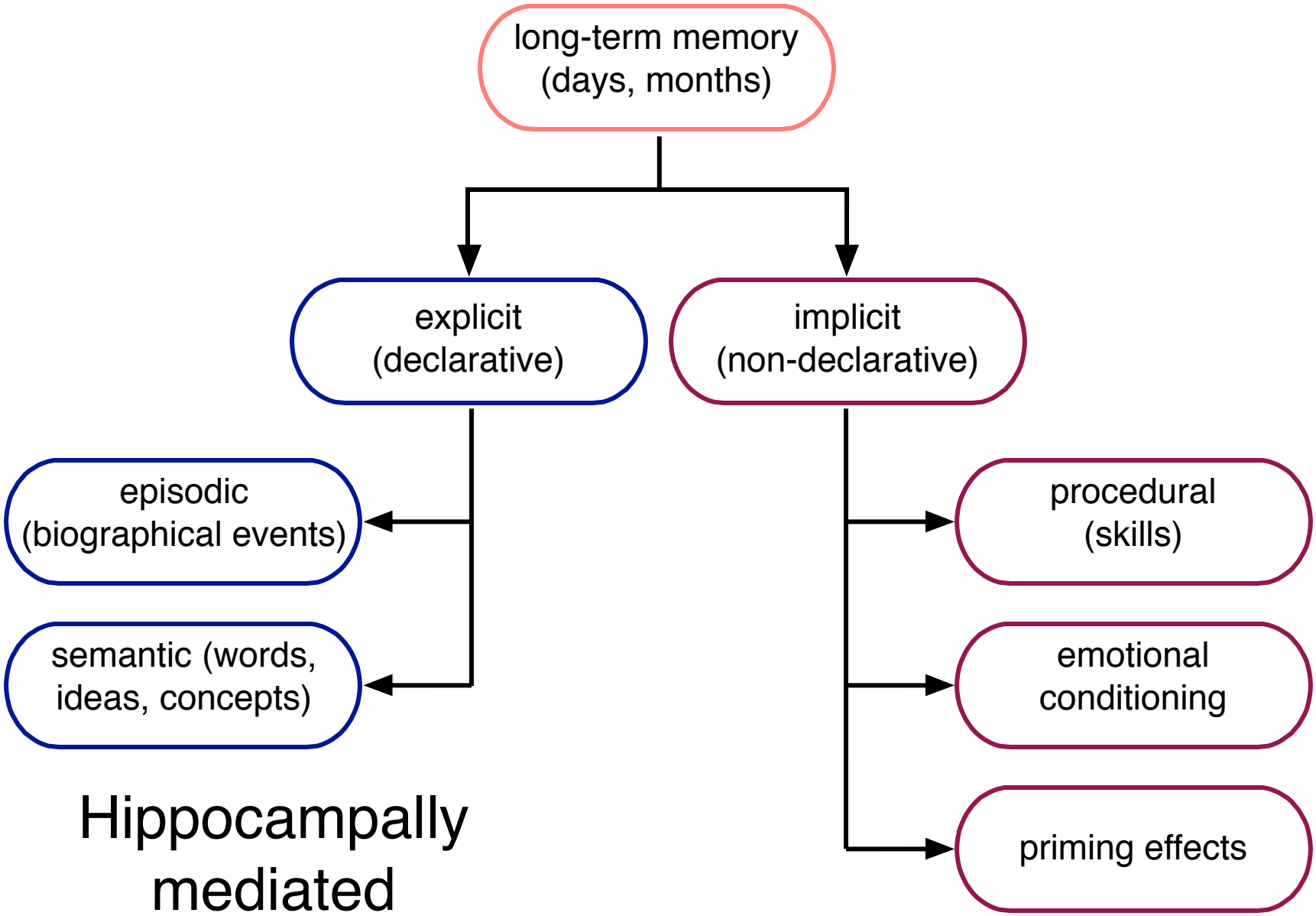
Remote memory -

- memory of events many months ago
- distributed in neo-cortex, no longer requires hippocampus for retrieval



GK Aguirre 2013

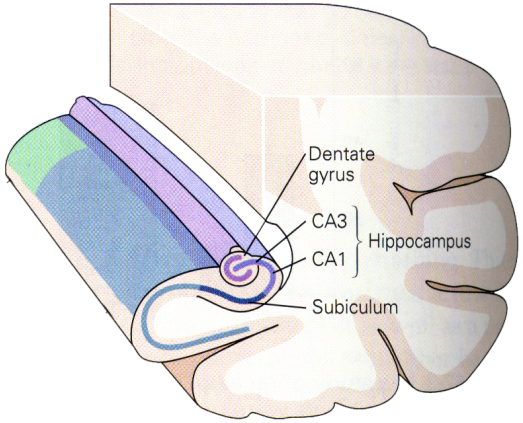
Memory systems - type

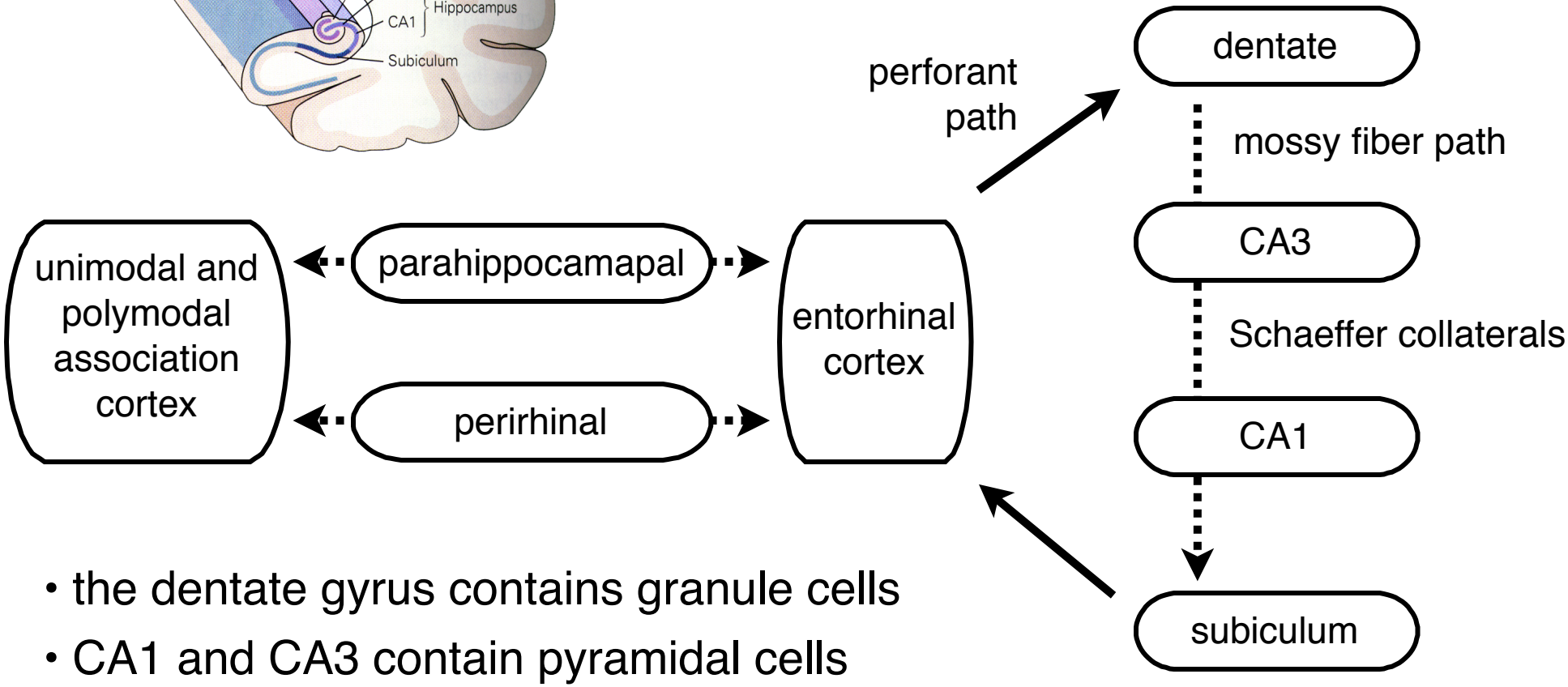


Hippocampally mediated

GK Aguirre 2013

Long-term memory anatomy

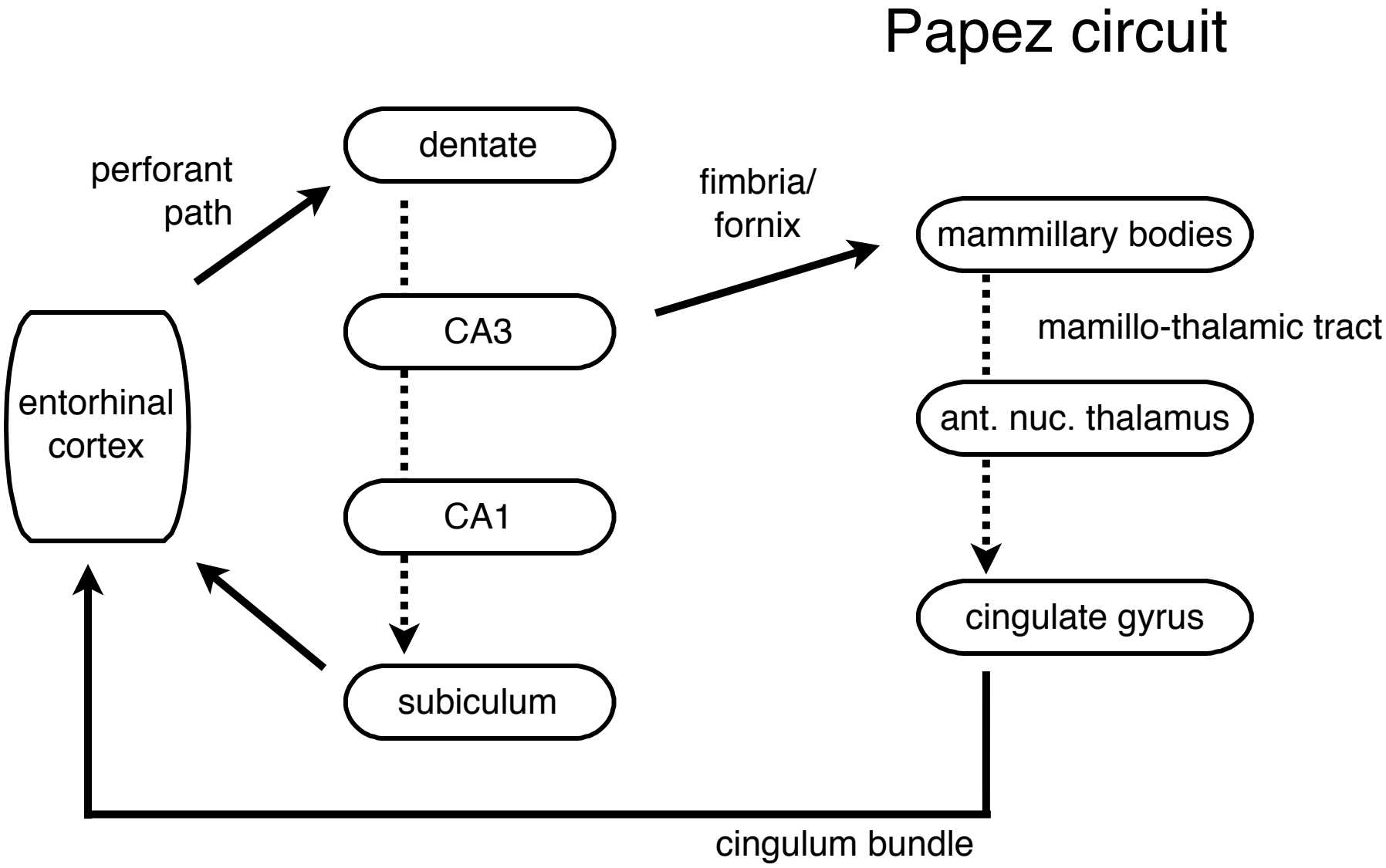




- the dentate gyrus contains granule cells
- CA1 and CA3 contain pyramidal cells
- The CA regions are very sensitive to hypoxia

GK Aguirre 2013

Long-term memory anatomy



GK Aguirre 2013

Amnesias

Hippocampal amnesia -

- Antereograde amnesia (unable to form new memories)
- Temporally graded retrograde amnesia (memories of events > 6 months before injury intact), intact working-memory
- Bilat hippocampal damage (sx, anoxia, HSV, limbic encephalitis)

Korsakoff's amnesia -

- Similar to hippocampal amnesia with marked confabulation
- Chronic thiamine (B_1) deficiency, paraventricular hemorrhages, particularly in mamillary bodies and medial dorsolateral thalamus

Transient global amnesia -

- Sudden onset antereograde amnesia of several hours duration, monophasic
- Believed to be due to spreading depression in mesial-temporal lobes

GK Aguirre 2013

Normal aging

Normal aging has characteristic changes in cognition:

Memory retrieval -

- Tip-of-the-tongue phenomenon
- Recall is *effortful*, patient is *aware* of difficulty, and is usually ultimately *successful* (after a delay)

Speed of processing -

- Steadily slows
- Affects all cognitive domains (Timothy Salthouse, 1996 Psychological Review)

Preservation of vocabulary -

- The exception is vocabulary, which continues to improve
- Performance on reading irregular words (part of the National Adult Reading Test) is preserved even in early stages of dementia

Exercise before the age of 50 predicts better cognition

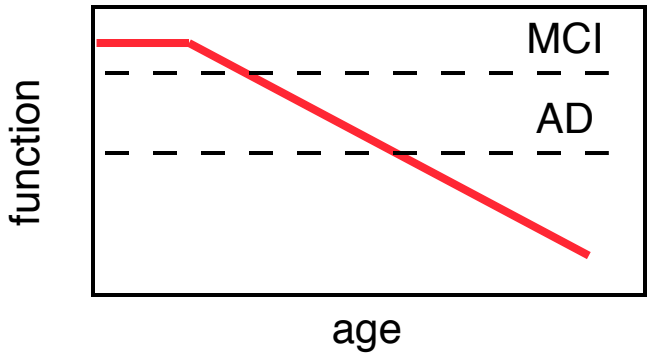
GK Aguirre 2013

Mild cognitive impairment

Patients with dementia transition through mild impairment

criteria

1. Memory complaint
2. Normal general cognition
3. Normal activities of daily living
4. Objective memory impairment for age
5. Not demented



Specific declarative memory tests far more sensitive than MMSE

Incipient atrophy of the mesial-temporal lobes can be seen

Minimal pathological hallmarks of Alzheimer's disease are present

Progression to dementia ~15% per year (compared to 1-2% for age matched controls), although only 75% ultimately become demented over 10 years

GK Aguirre 2013

Alzheimer's disease - clinical features

10% of individuals > 65 affected, 40% of those > 85

DSM-IV criteria

1. Impairment in ≥2 cog domains (incld. memory)
2. Aphasia, apraxia, agnosia, or impaired exec. fxn
3. Deficits interfere with activities of daily living
4. Gradual and continual decline
5. Other causes of dementia excluded

Initial memory loss is of recent events (hippocampally mediated)

- repeats self in conversation
- confusion regarding day and date
- generally unaware of difficulty

Remote memory and short-term (working) memory is preserved initially

GK Aguirre 2013

Alzheimer's disease - clinical features

Early features:

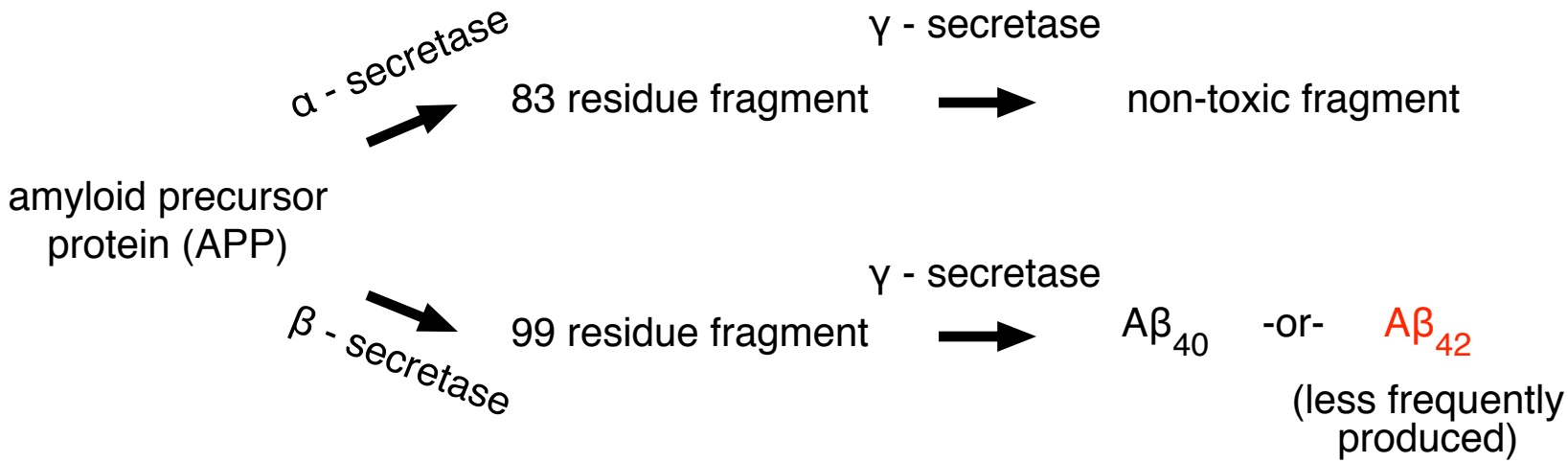
- subtle apraxia early, with "limb-as-tool" errors
- paucity of speech content (resembling transcortical-sensory aphasia)
- anomia with circumlocutions
- paranoid / delusional behavior in 50%
  (suspicions of infidelity common)

Later features:

- nocturnal wandering
- Pseudo-bulbar affect
- myoclonus (in up to 20% in late stages)
- hallucinations (10% of cases)
- Balint's syndrome (with predominant parietal atrophy)

GK Aguirre 2013

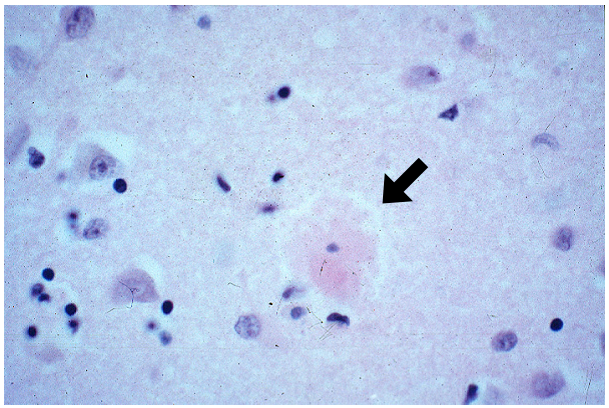
Alzheimer's disease - amyloid plaques



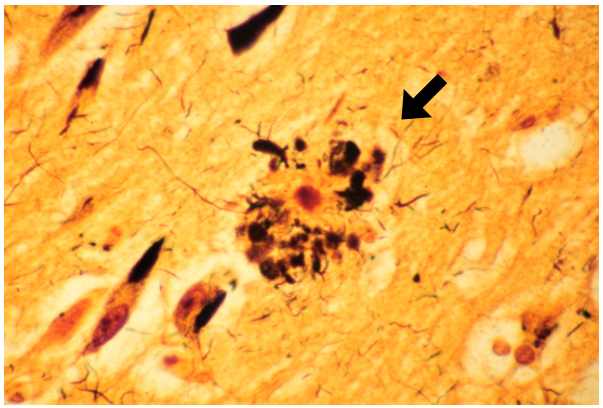
$A\beta_{42}$ is the major constituent of cerebral amyloid plaques

Neuritic plaque burden correlates with dementia (diffuse do not)

Plaques are non-specific and *can be seen* in normal aging



diffuse plaque (congo red)

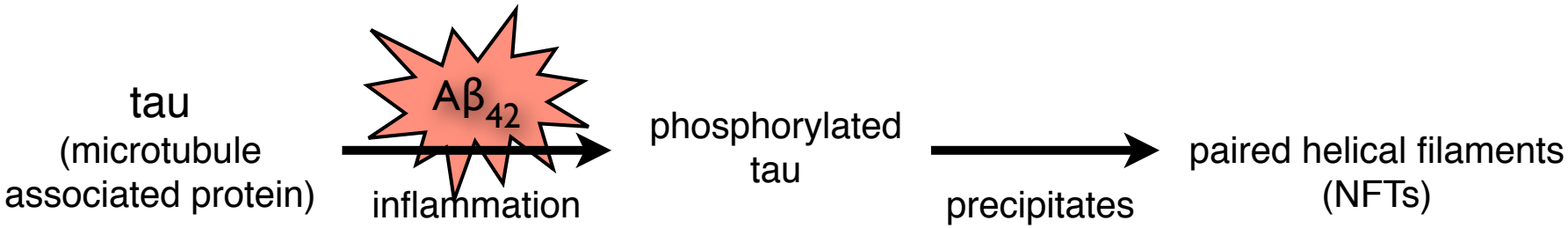


neuritic plaque

GK Aguirre 2013

Alzheimer's disease - tangles

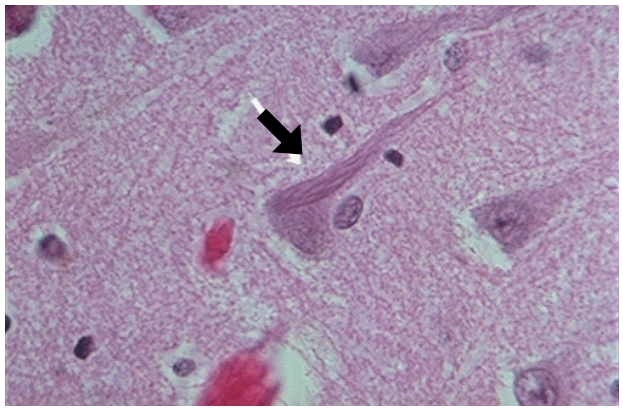
Neurofibrillary tangles (NFTs) appear first in entorhinal cortex and hippocampus, followed by limbic and then neocortex



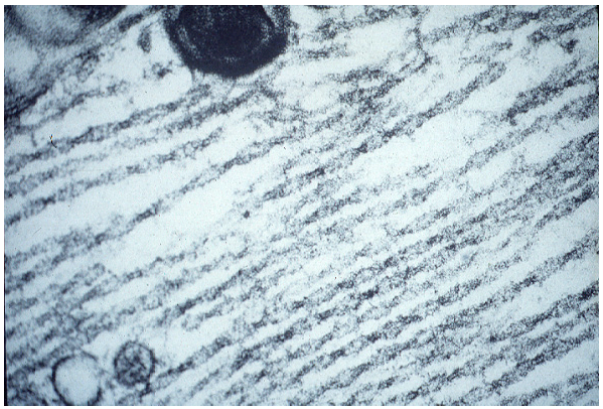
Tau (chr 17) comes in two flavors: a 3 exon repeat or 4 exon repeat

AD is a tauopathy with a mixture of the 3R and 4R isoforms

Tangles *are not* seen in normal aging



neurofibrillary tangle



paired helical filaments (EM)

GK Aguirre 2013

Alzheimer's disease - diagnostic tests

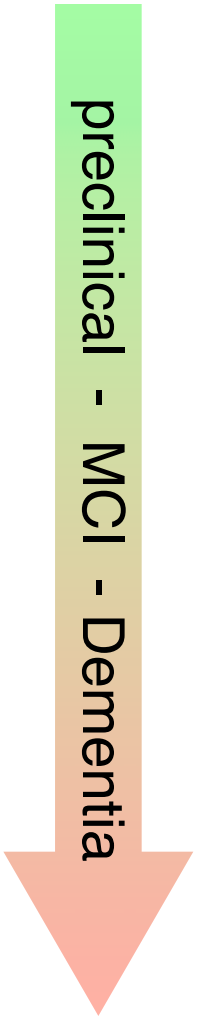
Amyloid imaging: Pittsburgh compound B (PiB) PET imaging of beta-amyloid binding. 86% sensitive and 92% specific in predicting MCI conversion to AD.

CSF: *reduced* $A\beta_{42}$, *increased* tau sensitive for AD (mechanism: dysfunctional clearing of Aβ into CSF)

PET/SPECT: bi-temporal and parietal hypometabolism

MRI: early mesial-temporal atrophy, next atrophy in association cortex, particularly parietal cortex

Psychometrics: impairments in supra-span list learning, Boston naming task performance, praxis



caveats

1. These tests are for research classification, not general clinical use
2. Diagnosis is *still* based on clinical impression
3. Can be useful in distinguishing AD from other dementing illnesses

GK Aguirre 2013

Alzheimer's disease - genetics: APP

5% of cases of AD are familial -- younger age of onset, autosomal dominant inheritance

APP is coded on chromosome 21

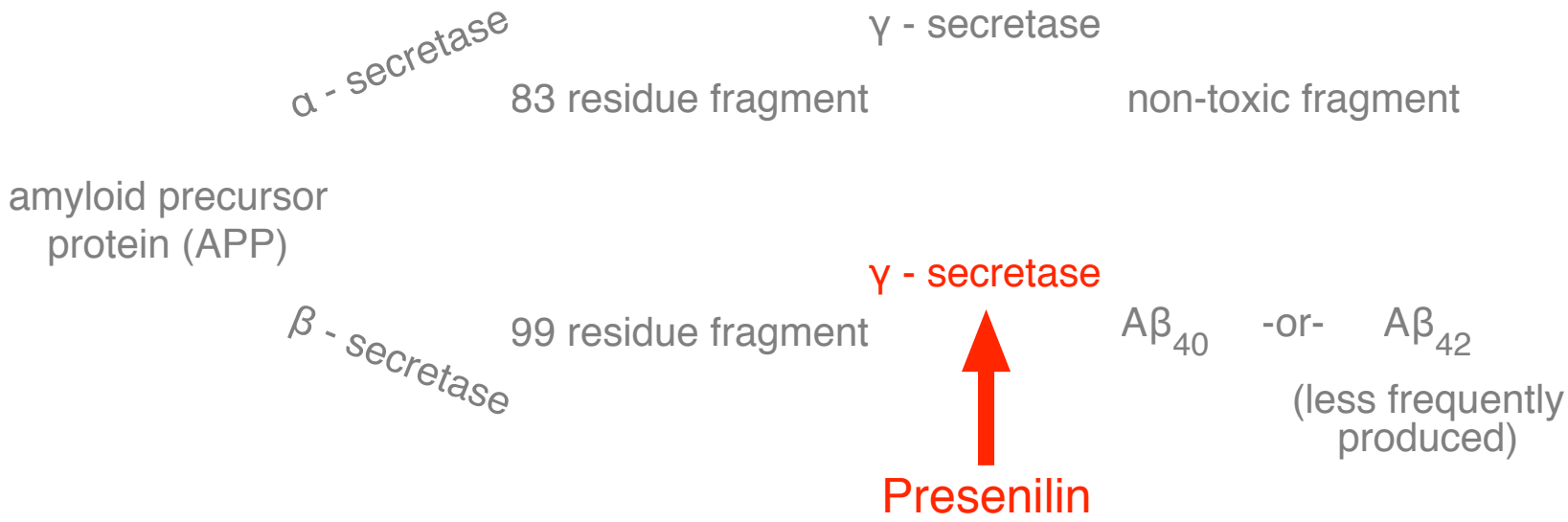
Mutations here an uncommon cause of familial AD (<10% of cases)

May predispose to creation of toxic proteolytic fragments

Down's Syndrome (trisomy 21) is associated with premature formation of AD pathology, perhaps because of a gene dosage effect

GK Aguirre 2013

Alzheimer's disease - genetics: Presenilin



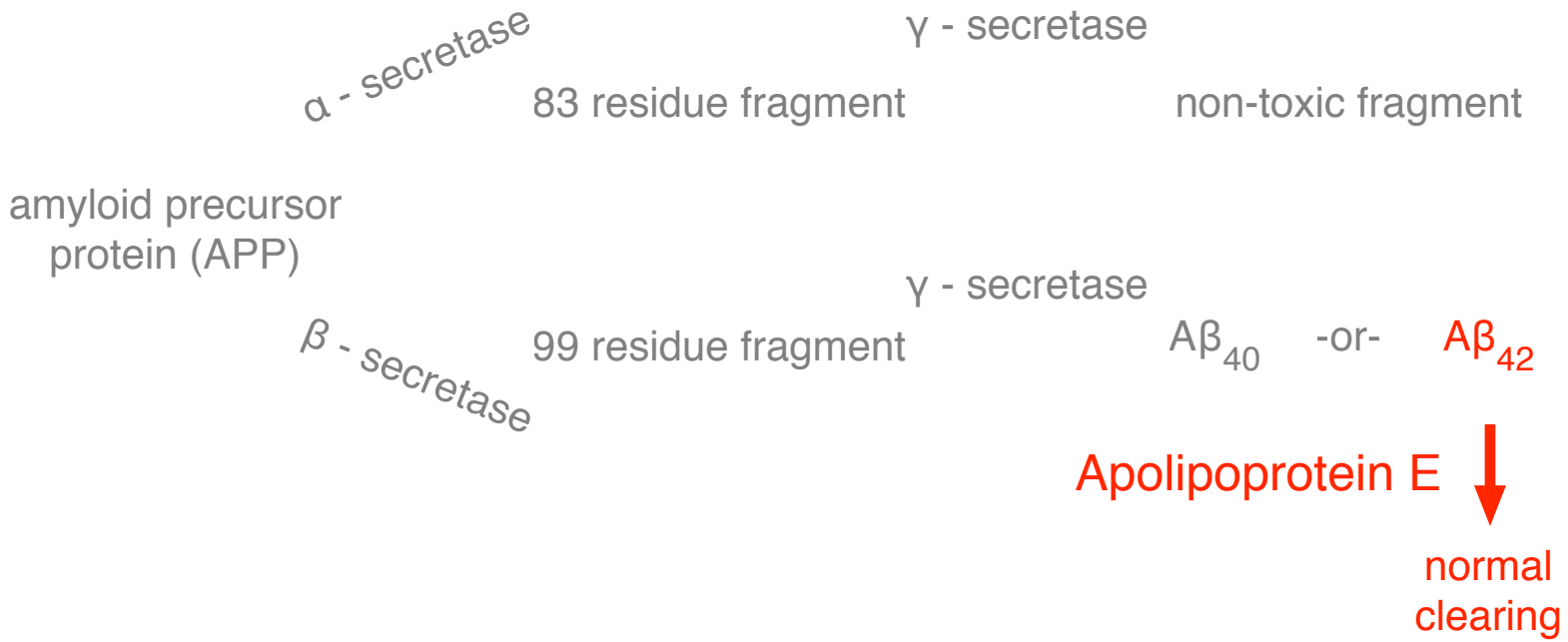
Mutations of Presinilin 1 (chromosome 14) account for ~50% of familial (early onset) AD

Mutations of Presinilin 2 (chromosome 1) account for 1% of familial (early onset) AD

The Presinilins are thought to act as co-factors for the γ - secretase complex

GK Aguirre 2013

Alzheimer's disease - genetics: Apoε



Variations in ApoE (chromosome 19) account for 50% of sporadic, late-onset AD (not familial)

The ε4 allele confers the greatest risk (homozygus for ε4 gives >90% chance of developing AD by age 85)

ApoE plays some role in the deposition and clearance of Aβ

GK Aguirre 2013

Alzheimer's disease - treatment

Decreased acetylcholine (ACh) activity is the primary neurochemical change in AD

(recall: nucleus basalis of Meynert, diag. band of Broca)

Acetylcholinesterase inhibitors (AChEIs) -

- Galantamine, Donepezil, Rivastigmine
- Delay loss of independent function by about 12-18 months, benefit appears greater if started earlier
- Recently approved larger dose of Donepezil (23mg daily) has claimed 50% greater efficacy, but increased side effects

- Common side effects: GI upset (~10%), insomnia, vivid dreams
- Less common: bradycardia causing orthostasis, muscle cramps

GK Aguirre 2013

Alzheimer's disease - treatment

NMDA receptor antagonist -

- Memantine (Nemenda®) - now approved for Alzheimer's at any stage (early or late)

Rejected (no benefit or harmful) -

- Vitamin E (increases stroke/MI risk)
- NSAIDS (ibuprofen)
- Estrogen
- Ginkgo biloba

Other -

- dextromethorphan / quinidine sulfate (Nuedexta®) for pseudo-bulbar affect
- Anti-depressants - avoid tricyclics because of anti-cholinergic effects, favor SSRIs
- Antipsychotics - favor atypical neuroleptics

GK Aguirre 2013

Frontotemporal lobar degeneration (FTLD)

Onset in the 50s, relative spared memory, marked personality Δ

Three classic clinical subtypes -

- Behavioral variant - apathy, disinhibition, poor hygiene
- Primary progressive aphasia - effortful, non-fluent speech
- Semantic dementia (temporal variant) - poor comprehension, anomia, associative agnosia

personality Δs

1. Disinhibition, reckless behavior
2. Stereotyped, ritualized behaviors
3. “Gramophone” (catch-phrase) syndrome
4. Preference for sweet foods
5. Item hoarding

Gross Pathology -

- Usually (70%) unilateral atrophy, in frontal or anterior temporal regions with good correspondence with behavioral changes

GK Aguirre 2013

Frontotemporal lobar degeneration (FTLD)

Recent work has shown that clinical FTLD is the common manifestation of several different molecular processes:

Typical FTLD is a *tauopathy* with the 3R isoform. Intracytoplasmic inclusions (Pick bodies) contain tau and/or TDP-43 (transactive response DNA-binding protein-43)

Atypical FTLD and *FUS*-opathy

FTLD-U has inclusions with *ubiquinated FUS* (fused in sarcoma), instead of tau or TDP-43. Progressive behavior and personality changes without aphasia or significant motor features, orbitofrontal and caudate atrophy (~10% of cases)

NIFID (neuronal intermediate filament inclusion disease) has inclusions with FUS and variable amounts of neurofilaments). Movement disorders accompany dementia.

FTLD with ALS is both a familial and sporadic presentation of dementia with alpha motor neuron degeneration with *FUS* inclusions and (in familial cases) a mutation in the *FUS* gene.

GK Aguirre 2013

Dementia with Lewy Bodies

Fairly common (20% of dementia cases); very rare familial cases

features

1. Parkinsonism
2. Fluctuations of attention and cognition
3. Well-formed visual hallucinations (>80%)

Supportive features:

- falls, syncope, transient loss of consciousness, delusions
- REM behavior disorder often seen early
- Hypometabolism in the occipital and parietal lobes on PET

Ubiquitin and α-synuclein Lewy-bodies / Lewy-neurites in cortex/ brainstem/substantia nigra

Prefer atypical neuroleptics for Rx of hallucinations (classic neuroleptics can worsen parkinsonism)

Dopamine / dopamine-agonists can worsen hallucinations

AChEIs can benefit cognition

GK Aguirre 2013

Corticobasilar Ganglionic Degeneration

Sporadic, onset in 60s, accounts for ~5% of Parkinson's clinic cases

features

1. Parkinsonism
2. Unilateral limb apraxia
3. Dementia

Initial unilateral parietal involvement:

- apraxia involving the opposite arm
- impairments with numbers, using a calendar, spatial position
- can be a cause of Balint's syndrome or posterior-variant cortical atrophy

"Alien hand" syndrome:

- a misnomer; different from the syndrome of callosal disconnection
- limb assumes postures and positions without the patient's awareness

CBGD is a tauopathy of the 4R isoform; astrocytic plaques seen

GK Aguirre 2013

Tau and Synucleinopathy Round-up

Tauopathy	Synucleinopathy
AIzheimer's disease (3R and 4R)	Parkinson's disease
Frontotemporal dementia (3R)	Dementia with Lewy bodies
Corticobasilar ganglionic degeneration (4R)	Multi-system atrophy
Progressive supranuclear palsy (4R)	
Argyrophilic grain disease (4R)	

(Refers to the 3 and 4 exon repeat isoforms of tau)

GK Aguirre 2013

FXTAS (Fragile-X tremor ataxia syndrome)

features

1. Progressive action tremor in both arms
2. Ataxia and falls
3. Dementia

} 90% have one or both of these

Average age of onset 60; affects 40% men who are premutation carriers, and some small fraction of women

Cognitive decline includes short-term memory loss, impaired executive function, impulsive personality

Length dependent neuropathy and incontinence may be present

MRI may show a bright middle cerebellar peduncle (MCP sign)

Apparently caused by mRNA toxicity, as opposed to Fragile-X syndrome in which loss of function of FMRP is responsible

Diagnose with Fragile-X genetic test (# CGG repeats on FMR1 gene)

GK Aguirre 2013

“Subcortical” cognitive impairment

Behavioral constellation with multiple etiologies

features

1. Psycho-motor slowing
2. Impaired concentration
3. Impaired reading
4. Forgetfulness

No focal cortical impairments

(aphasia, agnosia, etc)

Sleep disturbance (particularly sleep apnea), mood disturbance (depression), absence of aerobic exercise

Delayed effects of chemotherapy

Progressive-supranuclear palsy, multiple sclerosis

AIDS dementia complex -

- Late complication of HIV infection
- White matter pallor, vasculitis and giant cells on pathology

GK Aguirre 2013

Reversible causes of cognitive impairment

Evaluation of dementia begins with exclusion of these entities, although they are rarely responsible (< 1% of cases)

core tests

1. B_{12} level - subacute combined degeneration
2. TSH - mental slowing from hypothyroidism
3. Head CT - normal pressure hydrocephalus, sub-dural hematoma, frontal mass

* RPR, VDRL - neurosyphilis (no longer part of AAN params)

Other causes to consider -

- Depression causing pseudo-dementia
- Effects of medications
- Sleep apnea or other sleep disturbance

} common causes of memory complaints

- Systemic lupus erythematosus (ANA, anti-ribsosomal P Ab)
- Paraneoplastic (limbic encephalitis), Hashimoto's encephalitis
- Vasculitis

GK Aguirre 2013

Normal Pressure Hydrocephalus

features

1. Gait disturbance
2. Subcortical dementia
3. Incontinence

Hydrocephalus without sulcal enlargement on CT/MRI

"Gait apraxia" - foreshortened steppage and a shuffling quality, but with preserved arm swing and posture (aka *Magnetic gait*)

Gait impairments appear first or concurrently with urinary and cognitive changes. Incontinence linked to detrusor overactivity.

Approximately 50% of patients with probable NPH improve with shunt

Additional predictors of good response to ventriculoperitoneal shunt:

Dementia < 2 years

Gait disturbance first symptom

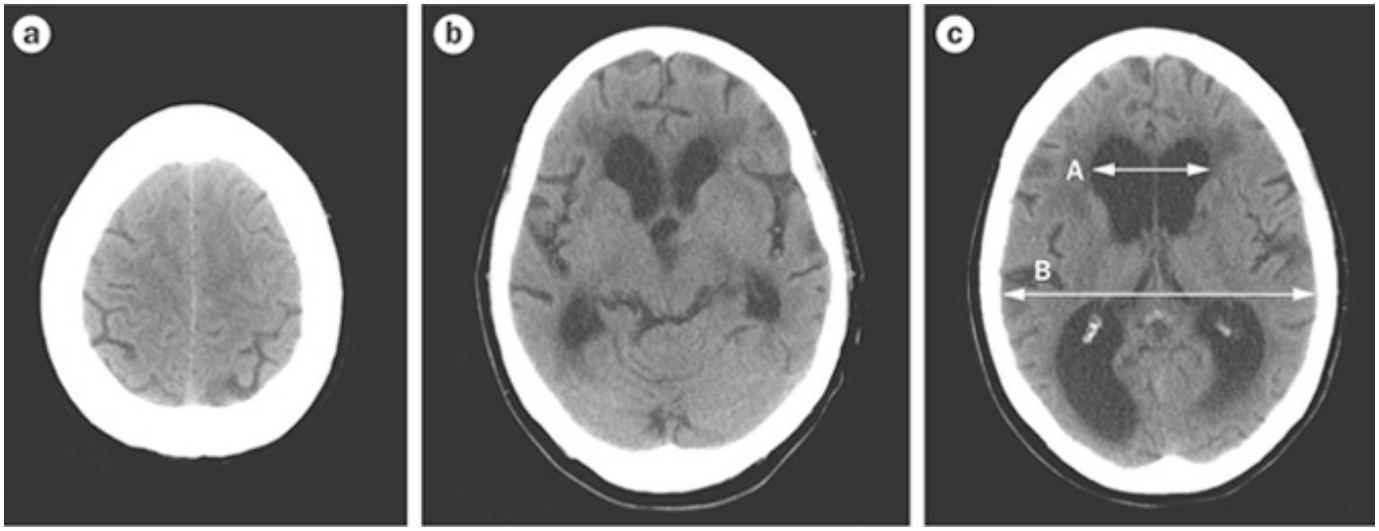
No history of EtOH abuse

Improvement in gait following large volume tap (30-50 ml)

GK Aguirre 2013

Normal Pressure Hydrocephalus - Imaging

- Ventricular enlargement out of proportion to sulcal atrophy
  - Evan's index > 30%
  - Rounding of frontal horns and thinning of callosum
  - Anterior temporal horn enlargement out of proportion to hippocampal atrophy
- Periventricular T2 hyperintensity (suggesting transependymal flow)
- Flow void in the aqueduct of Sylvius (T2 signal hypointensity)



Evan's index

$$\frac{A}{B} > 30\%$$

Morishita, T. *et al.* (2010) INPH and Parkinson disease: differentiation by levodopa response *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2009.195

GK Aguirre 2013

APPENDIX

Review:
Dysmnesias, reversible causes of cognitive impairment (B12 deficiency, hypothyroidism, neurosyphilis), vascular dementia, cognitive effects of AEDS and anti-cholinergics

GK Aguirre 2013

Dysmnesias

Ganser syndrome (pseudostupidity) -

- Approximate answers, disorientation, somatic conversion
- Dissociative psychiatric disorder of young males; occasionally the result of neurosyphylis

Capgras syndrome -

- Belief that a friend has been replaced by an imposter
- Seen in dementia and schizophrenia

Fregolli syndrome -

- Belief that strangers are familiar
- No good localization

Reduplicative paramnesia -

- Belief that an unfamiliar location is actually familiar
- Weakly associated with right parietal and frontal lesions

GK Aguirre 2013

Normal aging

Other neurological changes -

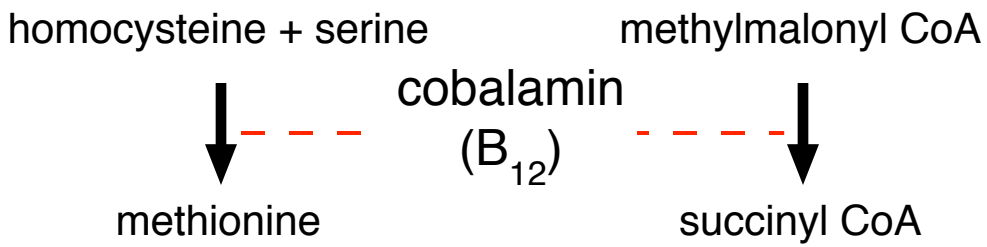
- Limited upgaze after age 60
- Decreased smooth pursuit
- Smaller pupils
- Mild increase in physiologic tremor
- Decreased high-frequency hearing

GK Aguirre 2013

B_{12} deficiency

features

1. Inattention / confusion
2. Somnolence
3. Apathy
4. Delerium



True dementia is rare, as is cognitive impairment without myeloneuropathy and/or optic neuropathy

Etiologies: Vegans, alcoholics, malabsorption, pregnancy, pernicious anemia

CBC with megaloblastic anemia, low B_{12} level, elevated methylmalonic acid and homocysteine (used to confirm borderline low B_{12})

Treat with 1000 μg IM qD x 1 week, then weekly x 1 month, then monthly for life

White matter degeneration irreversible after ~ 6 months

GK Aguirre 2013

Neurosyphilis

Tertiary syphilis results from chronic inflammatory process that, years to decades after initial infection, presents with meningitis, endarteritis or parenchymal involvement

Dementia paralytica is a chronic, progressive meningoencephalitis presenting 20-30 years after infection

features

1. Personality Δ (apathy, withdrawal, irritability) progressing to psychosis
2. Dementia (impaired judgment, confusion)
3. Periodic convulsions, progressive vegetative degeneration

CSF with > 10 WBCs, elevated protein, + CSF VDRL

Treat with PCN G, 2-4 million units IV q4 hours for 10-14 days

GK Aguirre 2013

Hypothyroidism

features

1. Slowed memory retrieval
2. Psycho-motor slowing
3. Impaired construction and visuoperceptual abilities

Primary hypothyroidism is common in the elderly

Look also for general depression, pathologically slowed deep tendon reflexes, swelling of hands and face, muscle cramps

Cognitive impairments may not be fully reversible, but can arrest decline with treatment

GK Aguirre 2013

Vascular dementia

2nd most common dementia clinically, 3rd pathologically, although it is a fairly ill-defined entity

Hachinski ischemic score

Abrupt onset	Stepwise deterioration
Fluctuating course	Nocturnal confusion
History of strokes	Preservation of personality
Focal symptoms	Depression, somatic complaints
Focal signs	Emotional incontinence
	HTN, atherosclerotic dz
1-2 points each	1 point each

≤ 4 points - 1° dementia

≥ 7 points - vascular

89% sens/spec to distinguish from AD

Forgetfulness is a relatively minor feature

20-40% of cases have a gradual decline, making discrimination from AD difficult

Be alert for CADASIL as the underlying cause

GK Aguirre 2013

Vascular dementia

Multiple pathologies -

- Chronic hypoperfusion of white matter
- Multiple lacunar infarctions (Binswanger's)
- Large artery disease

Treatment -

- AChEIs shown to be effective (Galantamine, Donepezil)
- Neurostimulants (Ritalin, Bromocriptine, Modafanil)
- Treat underlying vascular disorder / risk factors

GK Aguirre 2013

Anti-cholinergic agents

Many medications have anti-cholinergic properties and can cause memory loss and confusion

Class of medication	High anti-ACh	Alternative
antidepressant	tertiary tricyclics	SSRI
antihistamine	diphenhydramine	loratadine
Parkinson's	benztropine	L-dopa
GI agents	cimetidine	PPI
Antipsychotic	chlorpromazine	haldol

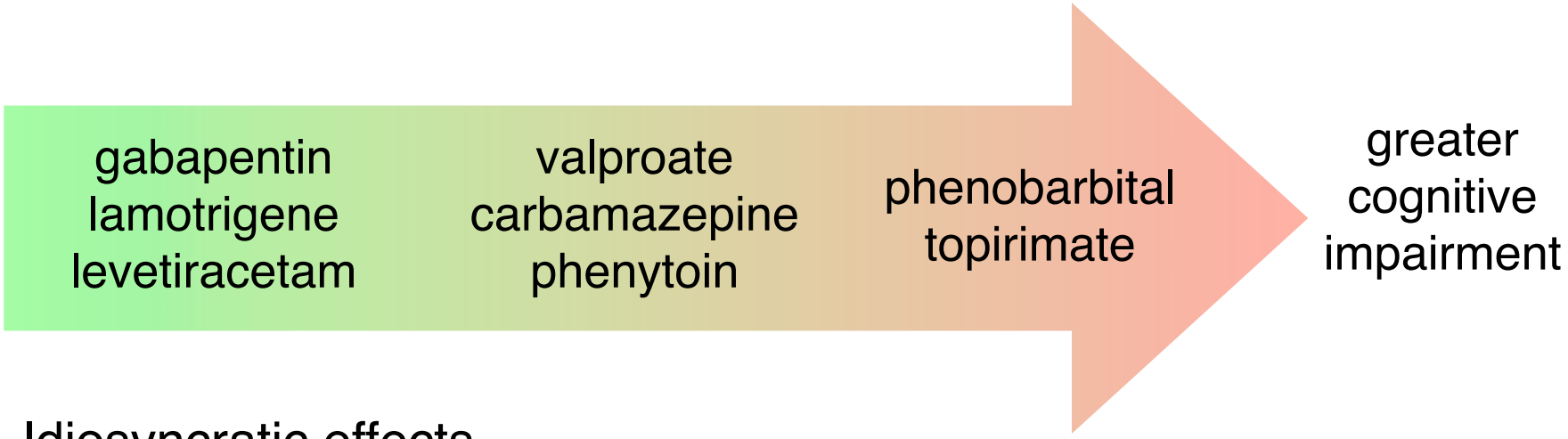
relative anti-ACh properties of TCAs

greater cognitive impairment

GK Aguirre 2013

Cognitive effects of AEDs

AEDs generally cause depressant effects in adults, but agitation and aggression in children



Idiosyncratic effects -

- gabapentin - actually *improves* mood in ~40% of patients
  no drowsiness until > 2400 mg/day
- topirimate - specific language impairment
- levetiracetam - increased aggression, psychotic behavior
- valproate - effective in the treatment of bipolar disease

GK Aguirre 2013