Notes: Damage & Disorders

Version:
12/02/12 - original version

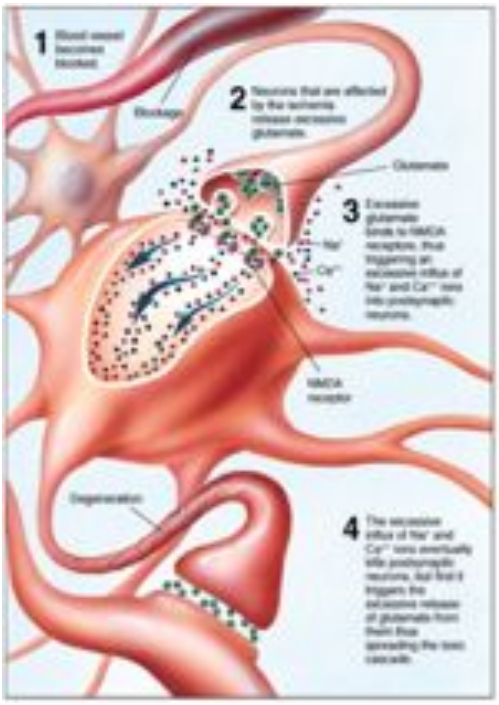
Damage

Stroke

crisis of _____ to neural tissue
US: 3rd leading cause of death, leading cause of adult disability
_____ - the area of dead/damaged tissue

cerebral _____
rupture of blood vessels
_____ - balloon like expanse in an artery

cerebral _____
disruption of blood flow
thrombosis - a plug or clot that develops in place
embolism - a plug or clot that develops elsewhere, travels through blood stream, lodges elsewhere
arteriosclerosis - narrowing of arteries



ischemic cascade

good but detailed: wikipedia.org/wiki/Ischemic_cascade

disruption of oxygen delivery causes energy crisis & failure to maintain cell homeostasis

fail to: _____

internal build up of Na+, permanent depolarization, glutamate release

fail to: clean up _____

causes over stimulation of post-synaptic neurons

influx and toxic buildup of _____ in post-synaptic neuron

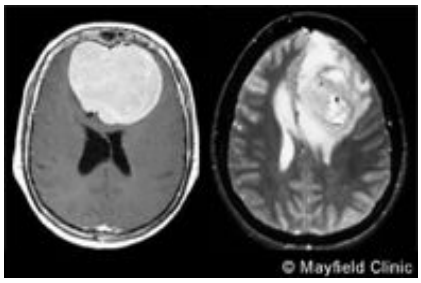
over-stimulation of next post-synaptic neuron, cycle repeats

damage takes days to develop

some areas more sensitive than others: hippocampus

Tumors

Benign (left) vs malignant (right) tumors



Source: www.mayfieldclinic.com/PE-BrainTumor.htm

_____

tumor originating in the meninges

usually benign, wrapped in a membrane

causes problems by displacing tissue

about 20% of brain tumors

malignant / metastatic

typically originate in other areas of the body

chemical and physical disruption of other cells

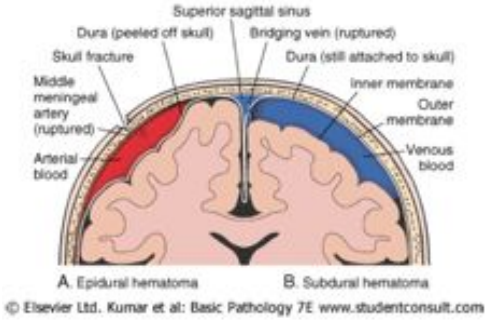
about 10% of brain tumors

symptoms: headaches, seizures, disruption of function

Closed head injuries

"Closed head injury" means the skull was not fractured

contrasts with "Open head injury" in which the skull was fractured or penetrated



_____ - damage to circulatory system

produces a hematoma (bruise)

_____

blow to head, loss of consciousness, no evidence of contusion

brain is colliding with skull

countrecoup - brain injury opposite location of impact ("sloshing")

repeated incidents can lead to long term deficits

currently a growing concern for football

the nature of the damage is not well understood

Infection

_____ - inflammation of brain due to the invasion of a microorganism

bacterial - syphilis, Lyme disease, malaria

viral - rabies, mumps, herpes

cause deficits by interfering with cell function and producing an inflammatory response

Neuron damage & regeneration

_____ - the ability of neuron configurations, and therefore the brain, to change with time and recover

critical to development, learning and recovery

Damage

_____

programmed cell death

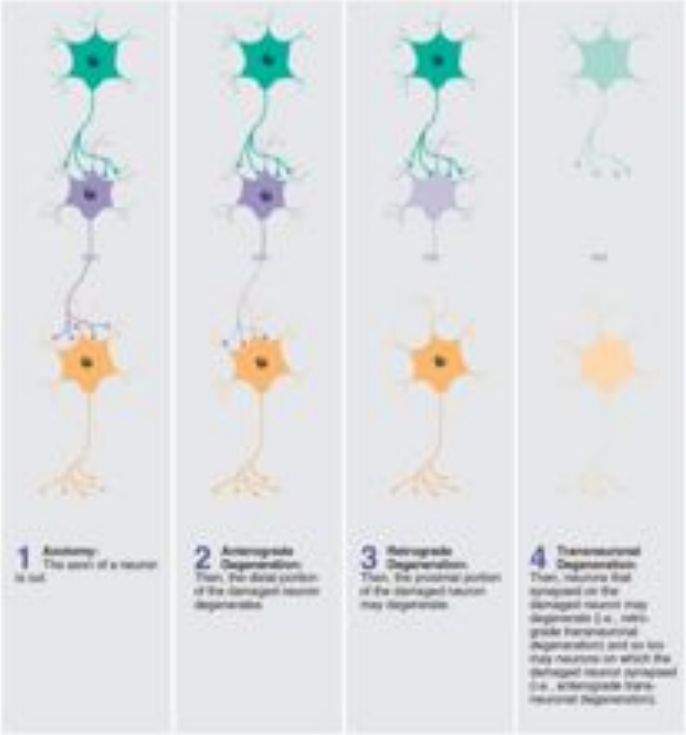
slow, orderly disintegration of cells, no inflammation, doesn't disturb neighboring cells

(Full review: Apoptosis in neurodegenerative disorders, Nature Reviews Mol Cell Bio, Mattson 2000)

_____

sudden, disorderly cell death

causes inflammation, disrupts neighboring cells



_____ degeneration

damage between cut and synaptic terminals

this is the distal portion of the neuron

_____ degeneration

damage between cut and cell body

this is the proximal portion of the neuron

_____ degeneration

when a neuron dies, other neurons that are

post-synaptic, or

pre-synaptic

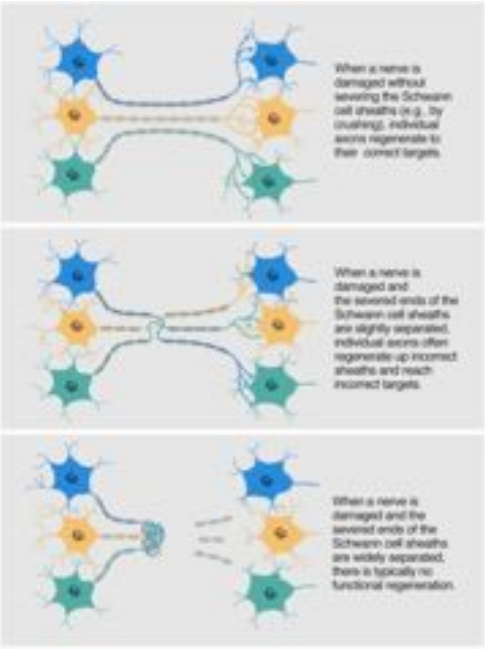
may also die

Regeneration

Unsuccessful in mature mammals and higher vertebrates

CNS - virtually non-existent

PNS - unlikely but possible



Regeneration in PNS

requires original _____ to be intact

neurotropic factors - chemicals that encourage tissue growth

CAMs - cell adhesion molecules, provide guidance

new growth may connect to incorrect targets

It is not the neurons themselves, but the environment

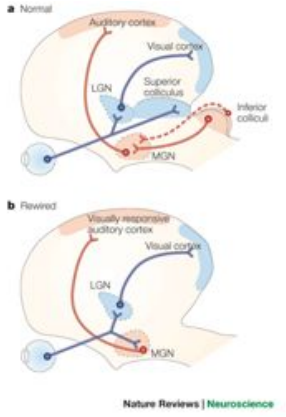
CNS neurons transplanted to PNS will regenerate

PNS neurons transplanted to CNS will not regenerate

Reorganization

Example 1: Reorganization in V1 following retinal lesions

In adult monkeys, remapping can occur within hours (Botelho et al, 2012)



Example 2: Rewiring neurons from the eye to the auditory cortex

In the developing ferret, input to MGN (auditory) is removed

MGN then "attracts" input from retinal ganglion cells

Visual stimuli produce activity in the auditory cortex

Source: Sur & Leamey, Nature Reviews Neuroscience, 2001

Example 3: In newly blinded individuals, auditory and somatosensory input is processed in formerly visual areas

Example 4: Phantom limb

somatosensory cortex that previously received input from amputated arm begins responding to neighboring input

Example: touching a patient's cheek can feel like touching the amputated arm

Treatment & Recovery

_____ - return of original function in a damaged area

Example: after a stroke affecting the hand motor area, that tissue recovers and hand function returns

_____ - performing a function by newly learned methods using non-damaged areas

Example: after a stroke affecting the hand motor area, neighboring tissue learns to operate the hand

1. Reducing degeneration

apoptosis inhibition

nerve growth factors

estrogen (Review: Brann et al, 2007)

- females have better incidence/outcomes in neurological pathologies
- administration of estrogen improves post-stroke outcomes in rodents

2. Promoting regeneration

can be induced in CNS neurons by Schwann cells (Xu et al, 2004)

physical activity promotes adult neurogenesis in rodent hippocampus

3. Transplant

fetal substantia nigra cells for treating monkeys with Parkinson's disease-like symptoms

- limited success with humans

embryonic stem cells in rat damaged spinal cord improved mobility

4. Rehabilitative training

for hands, restrict the functioning limb to maximize use of impaired hand

for spinal cord injuries, facilitated walking

5. Prevention

rats raised in enriched environments are resistant to epilepsy, AD models, HD models

adults that are more cognitively active have less incidence of AD

Neuropsychological Diseases

A note on terms I use:

mechanism - what happens in the brain to produce the deficit ("pathophysiology")

cause - what genetic/environmental factors cause the disease to develop ("etiology")

Alzheimer's Disease

Most common cause of dementia, 4th leading killer of adults

Population

2000: 4 million Americans

2050: estimated 14 million Americans (Evans et al, 1990)

Typical onset at _____ years, but 10% of cases are _____

As the overall population grows older, more people are going to encounter the disease

Women are more likely to have it because they _____

Cause is unclear

Symptoms

initial - confusion, selective decline in memory

severe - can not: communicate verbally, understand words, recognize self or family, care for themselves

death due to _____ (i.e. can't properly chew food -> inhale particles -> contract pneumonia)

Diagnosis

Can only be diagnosed for certain in autopsy

Behavioral observation can identify dementia, but not AD as the specific cause

Mechanism: Neurons

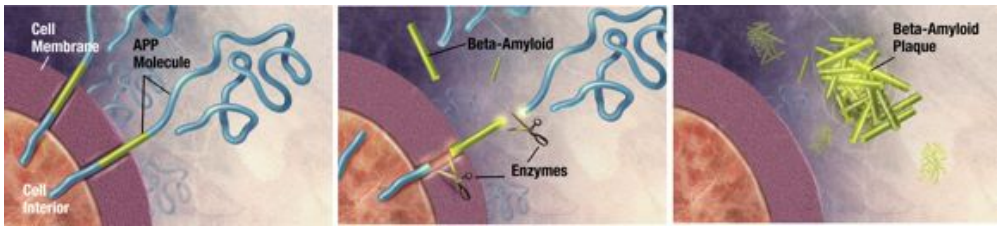
1. _____

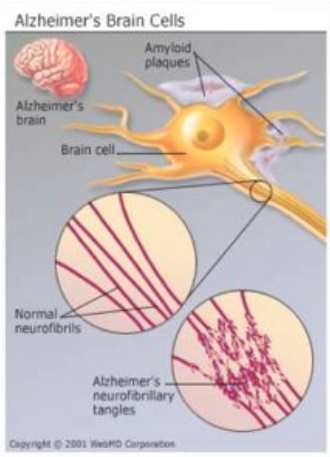
amyloid precursor protein (APP) - a normal protein in the neuron's cell membrane

amyloid beta - a portion of APP that is improperly clipped off

amyloid beta builds up as a plaque outside of neurons

genetic basis: a mutation in the gene for APP causes a 6x increased risk of early onset AD



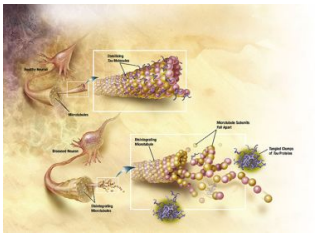


2. _____

microtubules - "railroad tracks" of the cell, transport molecules throughout cell

in AD, these become tangled

due to improperly formed tau proteins (the "railroad ties")



(right click and "View Image")

Mechanism: Brain

_____

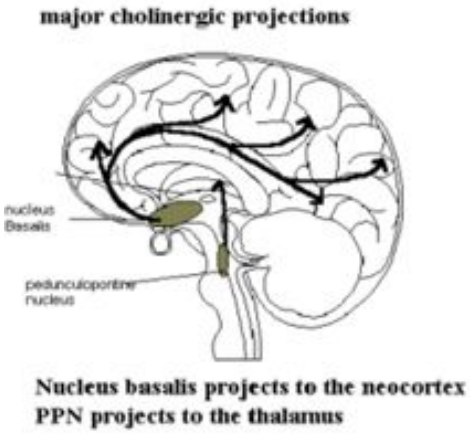
important neurotransmitter for learning & memory

produced in the nucleus basalis

and distributed throughout cortex

in AD, there is a decrease in nucleus basalis activity

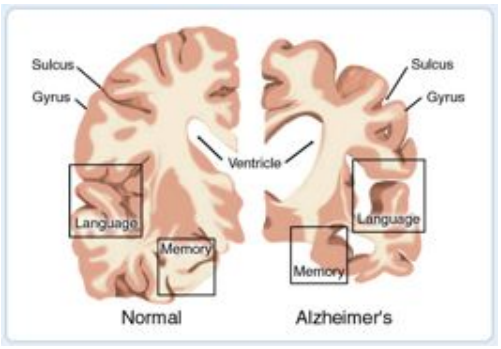
and levels of acetylcholine across the brain



Across the brain, there is widespread _____

Most pronounced in areas for

memory (hippocampus) and language



Animal model

_____ - genes from another species are introduced to produce a behavior or physiological condition

_____ - an animal with characteristics like a disease used to study causes and potential treatments

mouse model of AD

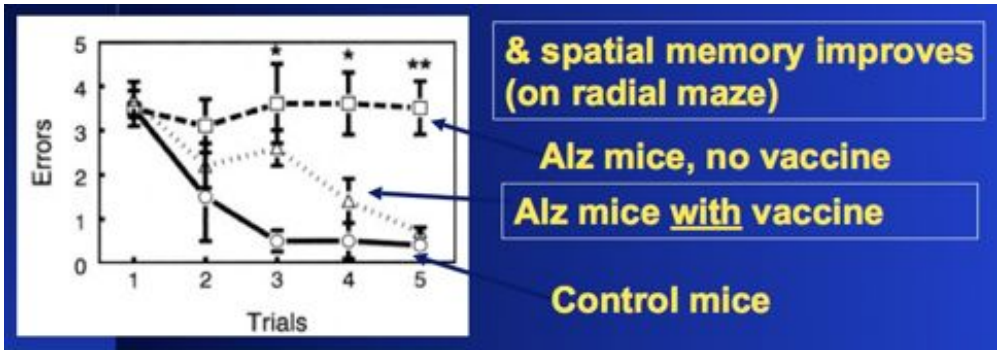
Only humans and some primates develop plaques, wild mice do not get AD

a mouse model was developed that develop plaques in the brain and diminished memory

vaccine (Schenk et al, Nature 1999)

a vaccine was developed that prevented/reduced plaques in mice and improved memory

produced encephalitis in human trials, never successful



Treatments

Working on a vaccine, but not successful in humans

monoamine oxidase inhibitors (MAOIs)

these prevent the breakdown to monoamines like _____

boast levels across the brain

not addressing a specific problem, just "turning up" neurotransmitters in general

NSAIDs (non-steroidal anti-inflammatory drugs)

aspirin, ibuprofen (Advil). analgesics and anti-fever. used for many issues like arthritis.

reduce inflammation in response to plaque damage

cholinesterase inhibitors

prevent the breakdown of acetylcholine

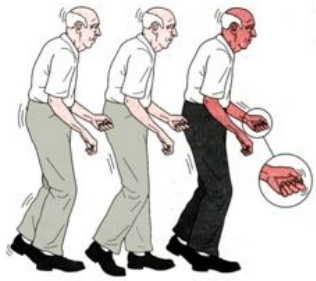
Treatment Summary: There are no working direct treatments, all address the disease _____

Parkinson's Disease

Population

Onset typically in 50s or 60s
Affects 0.3% of the population (approximately 1 million U.S. patients)
Most cases have unidentifiable causes
possible causes: genetics if onset before 50 years old, diet, smoking, rural areas, environmental toxins

Symptoms



20.2 CLASSIC SYMPTOMS OF LATE-STAGE PARKINSON'S DISEASE, including a stooped and rigid posture, shuffling gait, tremor, a masklike facial appearance, and "pill rolling" (inset). (After Markey, 1986.)

_____ at rest, typically in hand

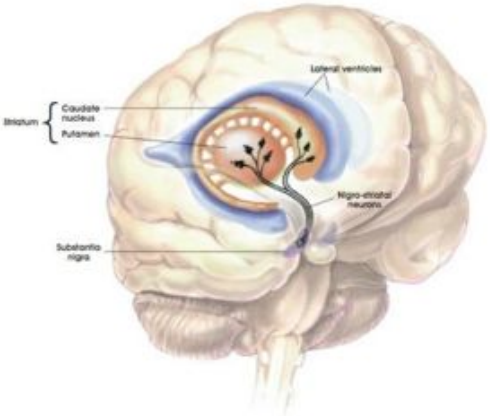
rigidity

_____ - inability to initiate movement

Cognitive symptoms (dementia) are not typical

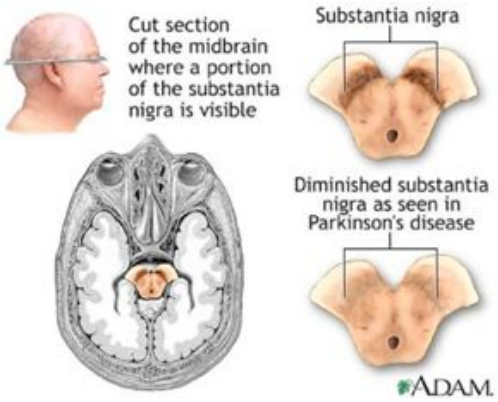
Mechanism

Review: substantia nigra distributes dopamine to the basal ganglia (in diagram, striatum is a major structures of the basal ganglia)



in PD, there is dramatic cell death in the substantia nigra

causes lack of dopamine in basal ganglia, therefore dysfunction in motor _____ and motor _____



Treatments

_____

a precursor to dopamine that can be absorbed through the blood brain barrier
problems: difficulty to dose, side effects, eventually loses efficacy (effectiveness)

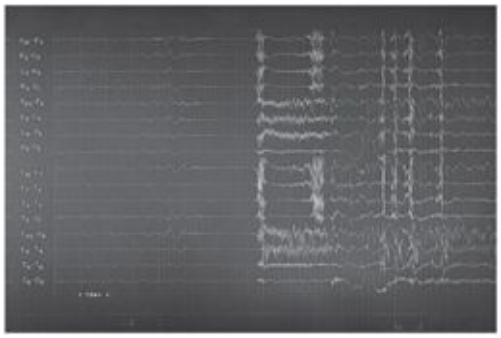
_____ of subthalamic nucleus (in basal ganglia)

- implant a "pacemaker" into an area of the basal ganglia
- patient can turn on and off and adjust settings
- can dramatically reduce tremor
- not clear how it is having its effect
- Movie: Deep Brain Stimulation (link pending)

Other Diseases/Disorders

(Note: The choice to cover Alzheimer's and Parkinson's in depth above was somewhat arbitrary, though these both affect large populations and tend to be in the forefront of the public's attention. The following diseases/disorders are covered briefly due to time constraints in the course, not due to less severity or social relevance.)

Epilepsy



Primary symptom is _____ (though not always)

- A burst of abnormal, self-reinforcing neural activity
- Usually generated internally, though sometimes by stimuli
- Convulsions - motor seizures
- Non-motor - can include loss of or shift in consciousness

Affects 1% of population

Diagnosed with EEG

Treated with anti-convulsant drugs and, if necessary, surgery

Huntington's Disease

Cause: Inheritable genetic mutation (single, dominant Huntingtin gene) with a reliable genetic test

Mechanism: With the genetic mutation, there is severe damage to striatum (basal ganglia)

Symptoms:

- initial - fidgety, restless
- final - jerky uncontrolled movement of limbs (_____), severe dementia
- death approx. 15 years after onset

Onset usually not seen until around 40 years old

If your parent has the gene, there is a 50% chance that you inherited. When, if ever, would you want to be tested?

Multiple Sclerosis

Unknown cause

Progressive _____ disease that attacks the myelin of the CNS

sclerosis - the hard scar tissue left behind

symptoms:

visual disturbances, muscle weakness, tremor, ataxia (loss of motor control)

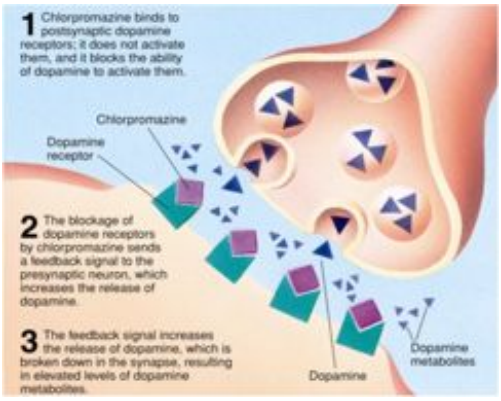
Periods of remission are common

Schizophrenia

Symptoms:

Positive symptoms: delusions, hallucinations, inappropriate affect, formal thought disorder

Negative symptoms: lethargy, social withdrawal, flat affect, alogia (lack of speech)



Theory: caused by overactive _____ in the brain

Increasing dopamine transmission exacerbates symptoms

Decreasing dopamine transmission is therapeutic

But for many reasons, dopamine is not the entire story

Treatments:

Chlorpromazine - Dopamine _____

calms agitated patients, activates withdrawn patients

Depression

5% of population suffer from unipolar (as opposed to bipolar) depression

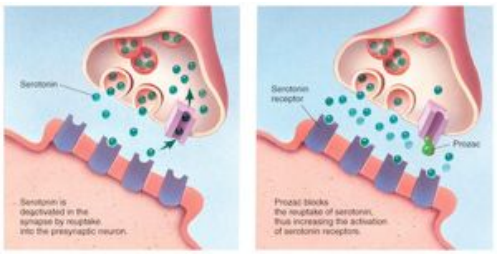
Cause

there is a genetic component to depression

stress is not a likely cause of depression

sparse evidence linking stress and depression

extreme stress is more likely to cause PTSD



Theory:

underactivity of _____ and _____ at synapses

Treatments

Monoamine oxidase inhibitors (MAOIs) - see Alzheimer's disease treatments for details

Tricylic antidepressants - Block reuptake of serotonin and norepinephrine

Selective serotonin reuptake inhibitors (SSRIs)

Prozac, Paxil, Zoloft

Not more effective than tricyclics, but less side effects

Selective norepinephrine reuptake inhibitors (SNRIs)

Other: light therapy, electroconvulsive shock therapy, chronic electrical stimulation

2002 study

MAOIs, tricyclics and SSRIs all get about a 50% improvement

control subjects have _____ improvement

2008 meta-study

_____ was 82% as effective as antidepressants in severely depressed individuals

antidepressants even less effective in mildly-moderately depressed individuals