Medical Neuropsychology: Neuropsychology of Human Organ Systems

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J. AUBREY BURHART

Never get sick

- Every organ system, if impaired, produces NP deficits.

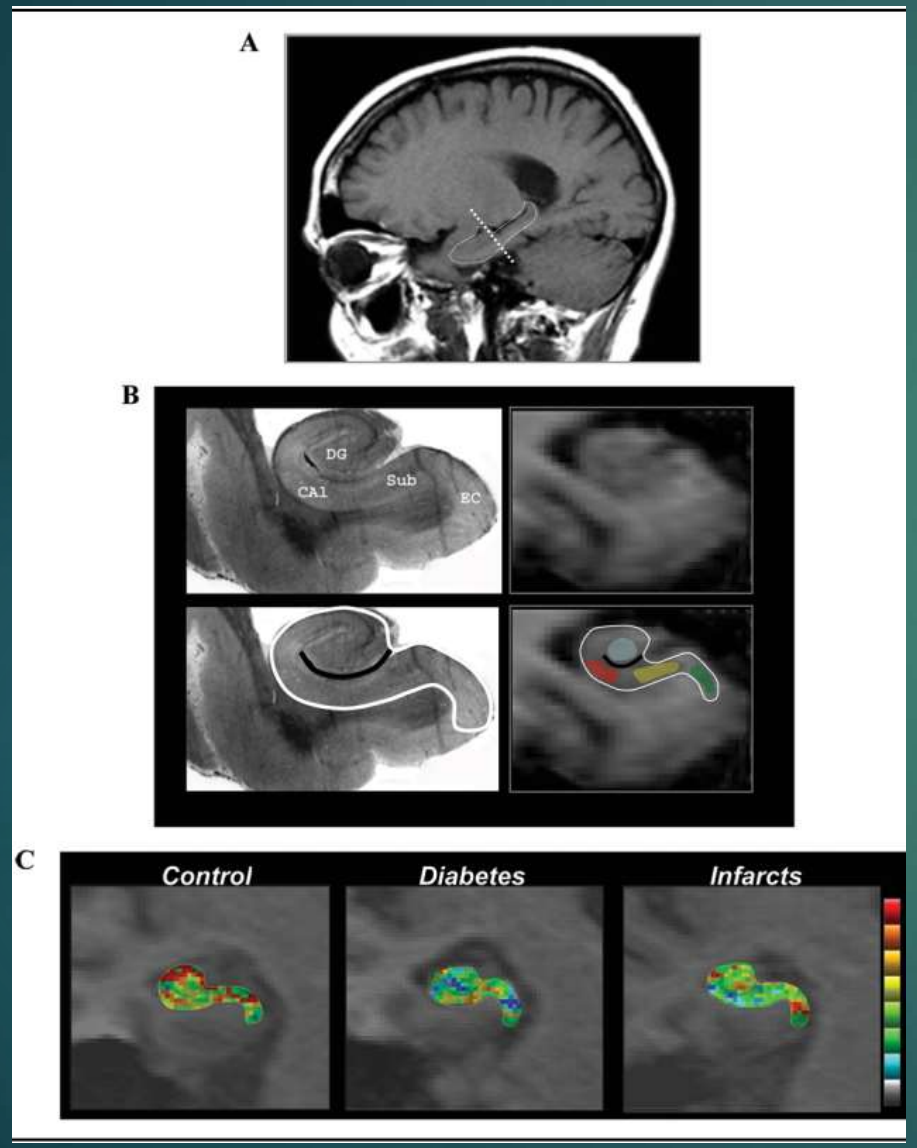
Cognitive Functioning in medical illness is essential for…

- Comprehending disease treatment and progression
- Making informed healthcare decisions
- Adhering to a treatment regimen
- Medication compliance
- Occupational success
- Maintaining social networks

Cognitive Neuroendocrinology: Glucose in the brain

- Glucose is primary energy source for cognitive activity
- Neurons can't store glucose; get glucose via blood circulation
- Conditions that affect glucose affect cognition
- Hippocampus/dentate gyrus is particularly sensitive to glucose availability; effects declarative memory; insulin promotes glucose utilization in hippocampus

Differential vulnerability to disease mechanisms



Red = greater Cerebral Blood Flow

- Diabetes & infarcts related to hippocampal dysfunction;
- Dentate gyrus linked to diabetes & blood glucose levels
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- CA1 & subiculum linked to infarcts & transient hypoperfusion
- AD targets entorhinal cortex

- Decrease in blood glucose increases dentate function, i.e. esp. exercise

Wu, et. al., Ann Neurol, 2008

Age Related Memory Decline

- The Dentate gyrus linked to diabetes implicated blood glucose as a pathogenic mechanism
- The Entorhinal cortex (CA1 & subiculum) linked to infarcts suggested transient hypoperfusion as a pathogenic mechanism
- These results show how diseases of late life differentially target the hippocampal formation, identify elevations in blood glucose as a contributing cause of age-related memory decline
- Even high normal blood sugar is considered a problem.

Cognitive Neuroendocrinology 2

- High density of glucocorticoid receptors in hippocampus
- Decreased declarative memory performance during any GC treatment (high dose prednisone Tx, Cushing's disease)
- Reduction of cortisol levels improves memory; high cortisol levels are toxic to hippocampal cells (i.e. PTSD)

Pulmonary Disorders: Oxygen in the brain

- Oxygen is crucial for brain function

- Brain consumes 20% of all oxygen used by body
- Effects of O deprivation: when partial pressure of arterial O is reduced to:
  - 75% of normal: Complex task performance decreases
  - 65% of normal: memory impaired
  - 50%, judgment impaired and unconsciousness may occur
  - 30-40%, death

Pulmonary Disorders 2

- Regional brain tissue O utilization is not homogeneous: some regions more vulnerable to hypoxia, esp. watershed areas (hippocampus, basal ganglia, cerebellum, occipital and frontal cortex)
- Hypoxic conditions: COPD, Asthma, Obstructive apnea, CO poisoning
- Anoxia produces significant neuropsychological deficits (memory, executive , agnosia, VS deficits, affective changes)

COPD

- Chronic Obstructive Pulmonary Disease (bronchitis, emphysema): 14 million in US
- COPD: progressive, degenerative disease: airflow obstruction, impaired gas exchange
- Risk factors: genetics, allergies, pulmonary infections, smoking
- Effects: SOB, poor exercise tolerance, loss of appetite, wgt change, fatigue;
- Predominant sx: dyspnea (distressing desire for air); hypoxemia (drop in arterial O content); hypoxemia leads to cognitive and affective impairments

COPD and Cognition 1

- COPD (hypoxemia) produces cognitive deficits (significant relationship between degree of hypoxemia and severity of NP deficits):
  - Executive deficits
  - Perceptual motor speed
  - Memory
  - Decreased FIQ, PIQ
  - Impaired attention

COPD in elderly: functional decline

- Study: 4,150 adults aged 50+ with and without COPD: found that individuals with severe COPD had significantly lower cognitive function than those without, even after controlling for confounding factors such as comorbidities.
- Using a 35-point cognition scale, the researchers found that scores among all patients with COPD declined on average by one point over the six-year period between 1996 and 2002.
- Mean cognition scores for those with severe COPD were significantly lower (0.9 points; p=0.01) than those without COPD.
- A 22 percent increase in the mean number of difficulties the severe COPD population would experience with daily tasks, or functional decline.

W. W. Hung , 2009

COPD and Cognition 2

- Oxygen therapy Tx results in reduction of severity of cognitive deficits

- Psychological distress and affective disorders common in COPD: 42% depression, panic attacks

Asthma

- Asthma: hyperreactive airways, intermittent, reversible attacks of airway obstruction
- 2-15 million adults in US

- Cognitive symptoms (due to hypoxic-induced brain abnormalities that occur during attacks) can include: processing speed, attention, memory

- Affective symptoms: 42% report anxiety, panic attacks

- Medications (prednisone, theophylline): little evidence of negative CNS effects

Obstructive Sleep Apnea

- OSA = frequent respiratory disturbance during sleep (snore and obstruct), excessive daytime sleepiness, fatigue
- 2-5% of females and 4-12% of men; 60% obese
- Neuropsychological and cardiovascular complications due to recurrent hypoxemia
- Cognitive deficits (due to severity of nocturnal hypoxia, daytime sleepiness): attention, memory, executive
- Personality changes, irritability, depression
- C-PAP Treatment: reduced daytime sleepiness, improved cognitive functioning (but not total)
- Sleep apnea is a risk factor for Alzheimer's disease

Sleep Apnea

- Grey matter deficits in the left parahippocampal gyrus and in the left posterior-parietal cortex with OSA. Deficits in the left posterior-parietal cortex were also shown to be associated with daytime sleepiness.

- Impairments in memory, attention, executive functions and constructional abilities and had higher sleepiness scores.

- Use of C-PAP: reverse these damages. After three months of treatment: GM-volume increase in the left anterior parahippocampal gyrus, which was associated with improved performance on tests of short- term memory and executive function.

CPAP vs BiPAP

- CPAP stands for continuous positive airway pressure; increases the pressure when you inhale
- BiPAP refers to Bilevel or two level positive airway pressure.
- While CPAP generally delivers a single pressure, BiPAP delivers an inhale pressure and an exhale pressure; provides more breathing assistance.
- Both machines are designed to make sure the users breathe a set number of times per minute

Sleep Loss

- The amygdala goes into overdrive on no sleep.
- This shuts down the prefrontal cortex, and thus prevents the release of chemicals needed to calm down the fight-or- flight reflex.
- If, for example, the amygdala reacts strongly to a violent movie, the prefrontal cortex lets the brain know that the scene is make-believe and to settle down.
- But instead of connecting to the prefrontal cortex, the brain on no sleep connects to the locus coeruleus, the oldest part of the brain which releases noradrenalin to ward off imminent threats to survival, posing a volatile mix.

M. Walker, Current Biology, 2007

Carbon Monoxide Poisoning

- Do not use gas generators indoors, hibachis, or keep car motors going in garage!

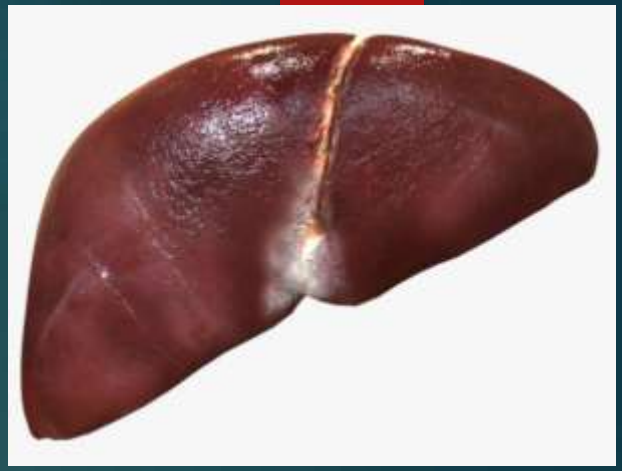
- CO poisoning is most common cause of poisoning death in US (40, 000 ED visits; 6000 deaths)
- Survivors often develop neuropsychological deficits, acutely or in delayed manner (40 days later)

- Structural abnormalities: demyelinization, cortical degeneration, cerebellar lesions, white matter lesions, hippocampal reduction, cortical atrophy, hypoperfusion, decreased CBF
- Deficits: memory, attention, irritability, personality changes, emotional lability, gait, extrapyramidal sxs, apraxia, VS, dementia

Pulmonary Disorders: Conclusions

- Patients with pulmonary disorders (COPD, OSA, asthma, CO poisoning), with concomitant hypoxia and hypoxemia, exhibit neuropsychological deficits
- Common NP deficits: attention, memory, VS, executive
- High rate of mood disorders and personality changes
- Hypoxia and hypoxemia are major sources of deficits
- PCPs are uneducated about NP effects of pulmonary disorders

Neuropsychological Dysfunction due to Liver Disease



- Liver: filter and metabolic factory

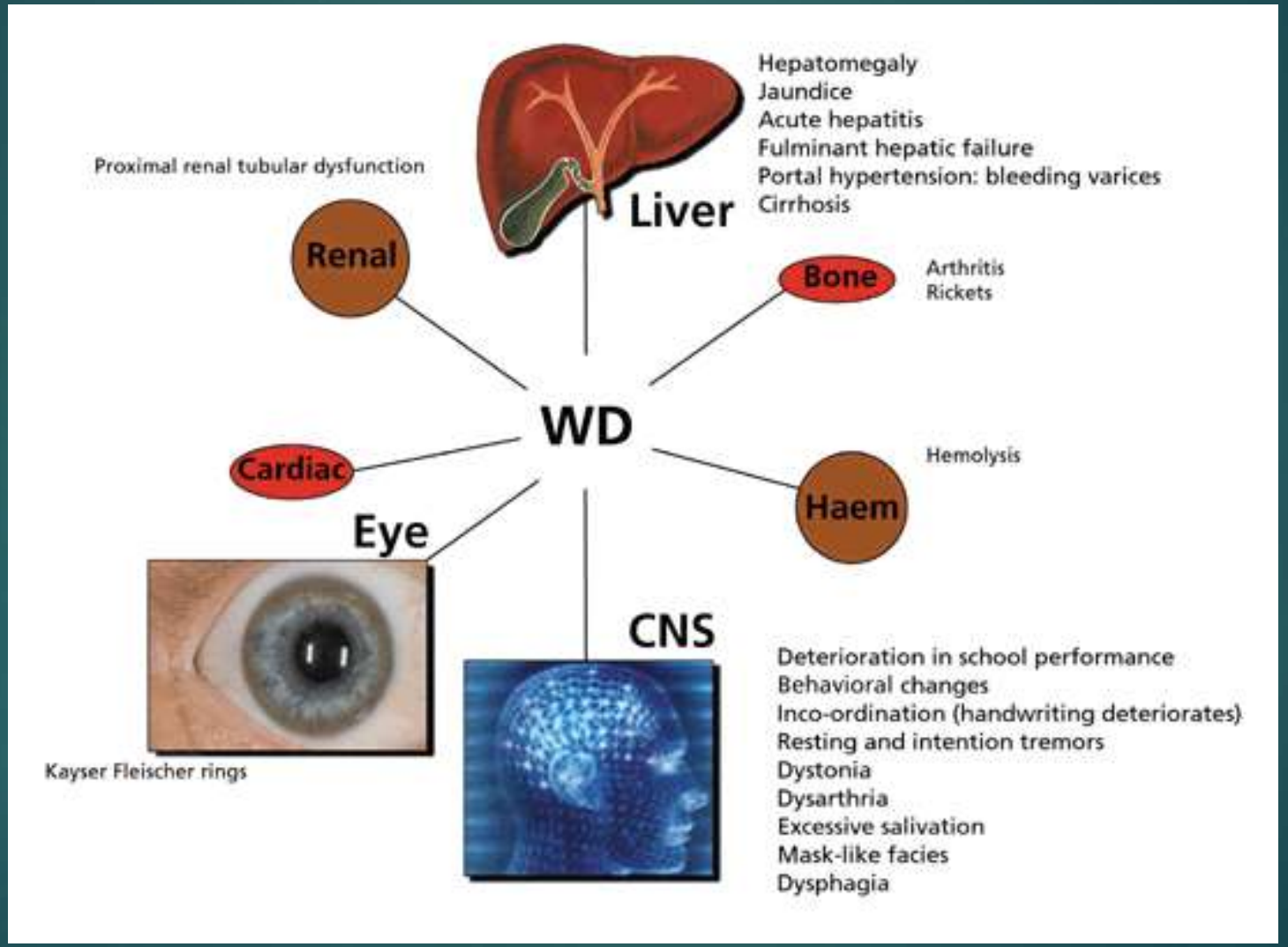
- Liver Diseases:
  - Hepatolenticular degeneration (Wilson's disease)
  - Cirrhosis (4th leading cause of death for ages 35-54) (morbidity, encephalopathy)

Wilson's Disease (Hepatolenticular Degeneration)

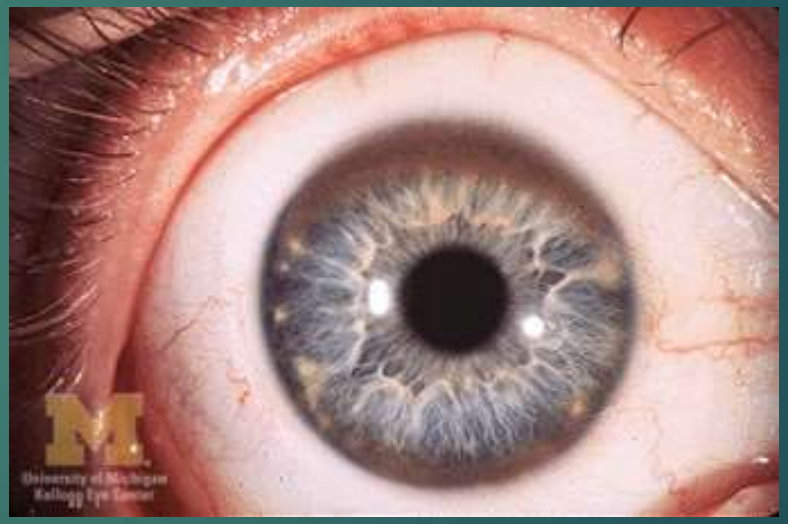
- Inherited (autosomal recessive) metabolic disease results from liver's inability to excrete copper (first in liver, then in brain); 5 per million, rare
- Childhood to young adulthood
- Acute hepatic failure (often fatal) or insidious chronic disease

- Chronic: HTN, esophageal bleeding, neurological and psychiatric sxs
- Neurological: intention tremor, rigidity, bradykinesia, dysarthria, gait, coordination; sensory ok
- Kayser-Fleischer rings in cornea
- Neuropsychological: TMT-B, BD, Symbol Digit deficits in neurological intact; Tx can reverse
- Treatment: chelating meds (D-penicillamine; trientine)

Wilson's Disease



Kayser-Fleischer Rings



Wilson's: Clinical sxs

Table 2. Clinical Features in Patients with Wilson Disease

Hepatic	• Asymptomatic hepatomegaly • Isolated splenomegaly • Persistently elevated serum aminotransferase activity (AST, ALT) • Fatty liver • Acute hepatitis • Resembling autoimmune hepatitis • Cirrhosis: compensated or decompensated • Acute liver failure
Neurological	• Movement disorders (tremor, involuntary movements) • Drooling, dysarthria • Rigid dystonia • Pseudobulbar palsy • Dysautonomia • Migraine headaches • Insomnia • Seizures
Psychiatric	• Depression • Neurotic behaviours • Personality changes • Psychosis
Other systems	• Ocular: Kayser-Fleischer rings, sunflower cataracts • Cutaneous: lunulae ceruleae • Renal abnormalities: aminoaciduria and nephrolithiasis • Skeletal abnormalities: premature osteoporosis and arthritis • Cardiomyopathy, dysrhythmias • Pancreatitis • Hypoparathyroidism • Menstrual irregularities; infertility, repeated miscarriages

Portal-Systemic/Hepatic Encephalopathy

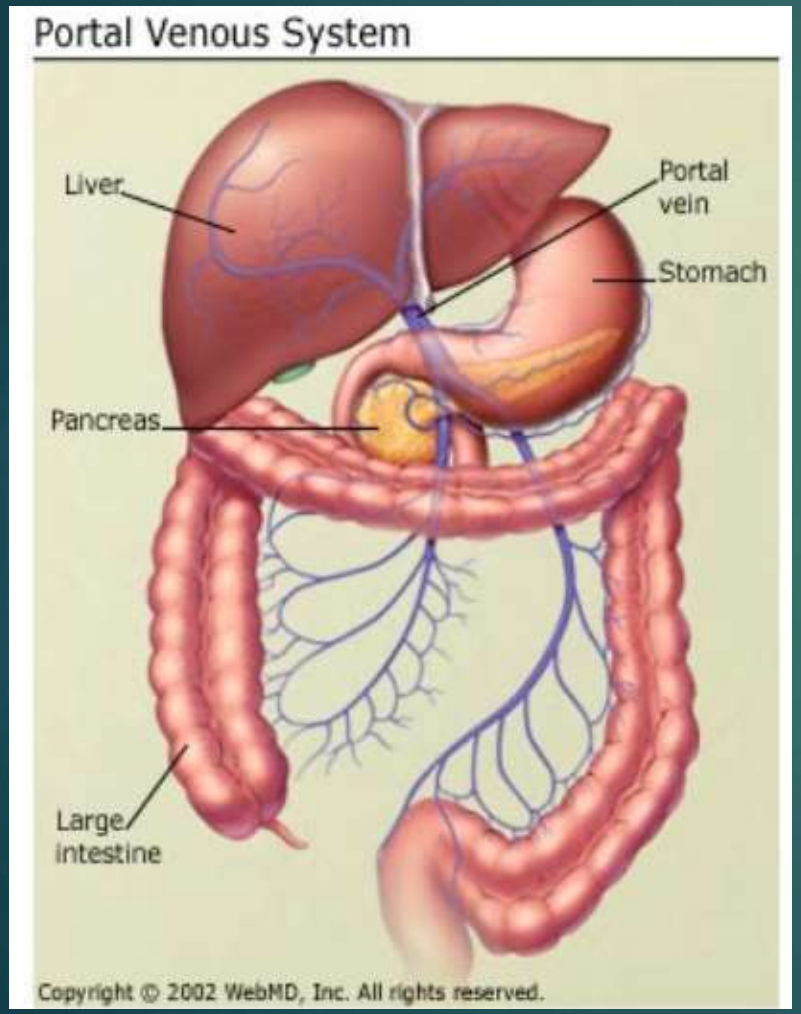
- Portal-Systemic or Hepatic Encephalopathy caused by postnecrotic ***cirrhosis*** **(**advanced stage liver disease due to alcohol, viral hepatitis, or metabolic or acetaminophen poisoning); warn teenage Tylenol SAs

- Increased slowing of liver blood flow, which leads to portal hypertension and reduced capacity to remove and detoxify toxins (esp. ammonia)

- PSE occurs as florid neuropsychiatric disorder, low grade chronic or acute condition.

- Sxs: day-night reversal, visual spatial deficits; non-synchronized, intermittent flapping motion at the wrists (asterixis); euphoria, depression, mental slowing, inappropriate affect, behavioral and sleep disturbance; apathy, stupor, coma; often diagnosed as anxiety reaction, psychotic depression

Portal hypertension



Portal hypertension is an increase in the blood pressure within a system of veins called the portal venous system. Veins coming from the stomach, intestine, spleen, and pancreas merge into the portal vein, which then branches into smaller vessels and travels through the liver.

Cirrhosis:
Neuropsychological and Neurological Deficits

- NP deficits due to cirrhosis independent of other liver disease symptoms (PSE)
- Deficits esp. in spatial, practic, and perceptual-motor: VS, handwriting, VIQ, memory
- Issue of some covariance with alcohol effects
- Neuropathology: frontal atrophy, cortical hypoperfusion, neuronal necrosis, demyelination
- EEG: triphasic wave pattern

Cirrhosis

- More than half of patients who have cirrhosis of the liver also display neurocognitive impairments such as short term memory loss

- 54 percent of 301 cirrhosis patients who were tested scored below the 10th percentile for their age and education on the RBANS; average score was 74. This is lower than the average score of patients with early-stage Alzheimer's disease.

Randall, 2010

Neuropsychology of Renal (Kidney) Disease

- Kidney: volume & composition of body fluids (clear substances from the blood, arterial pressure, cardiac function, endocrine function)
- Measures: GFR (glomerular filtration rate); CrCL (creatinine clearance), BUN (serum urea nitrogen)
- ESRD: End stage renal disease; need chronic hemodialysis; often due to hypertension
- ESRD sxs due to uremia (high level of nitrogen-type wastes in the blood): fatigue, anorexia, drowsiness, impaired attention, encephalopathy, EEG abnormalities

Renal Failure Treatment

- Most chronic renal failure is 2ndary to other medical diseases (esp. DM, HTN → cardiovascular↓; & autoimmune diseases) that may also independently adversely impact neurocognitive function
- Availability of chronic hemodialysis (HD), peritoneal dialysis (PD) and renal transplantation
- Choice:
  - PD = active role in TX
  - HD = passive role
    - NP testing on midweek nondialysis day to avoid acute effects of dialysis or of its lack during weekend

Impaired kidney function is a risk factor for cognitive decline in old age

- 886 older adults who participated in the Rush Memory and Aging Project, a group of community-dwelling seniors with a mean age of 81, all of them initially free of dementia.
- Poor kidney function assessed at the beginning of the study, was linked with a more rapid rate of decline in cognition over the next several years - not in visuospatial ability or perceptual speed, but in three specific areas: episodic, semantic and working memory.
- Underlying vascular problems, such as diabetes and hypertension, may account for the association between kidney problems and cognitive decline.

Aron Buchman , 2009

Chronic Renal Failure

- Gradual developing uremic syndrome (high nitrogen wastes)
- Advanced uremia results in mental status abnormalities and NP deficits (in prehemodialysis era)
  - Lethargy, confusion
  - Inability to concentrate
  - Slowed thinking, decreased alertness
  - Memory deficits, attentional deficits
  - Intelligence decline

Anemia

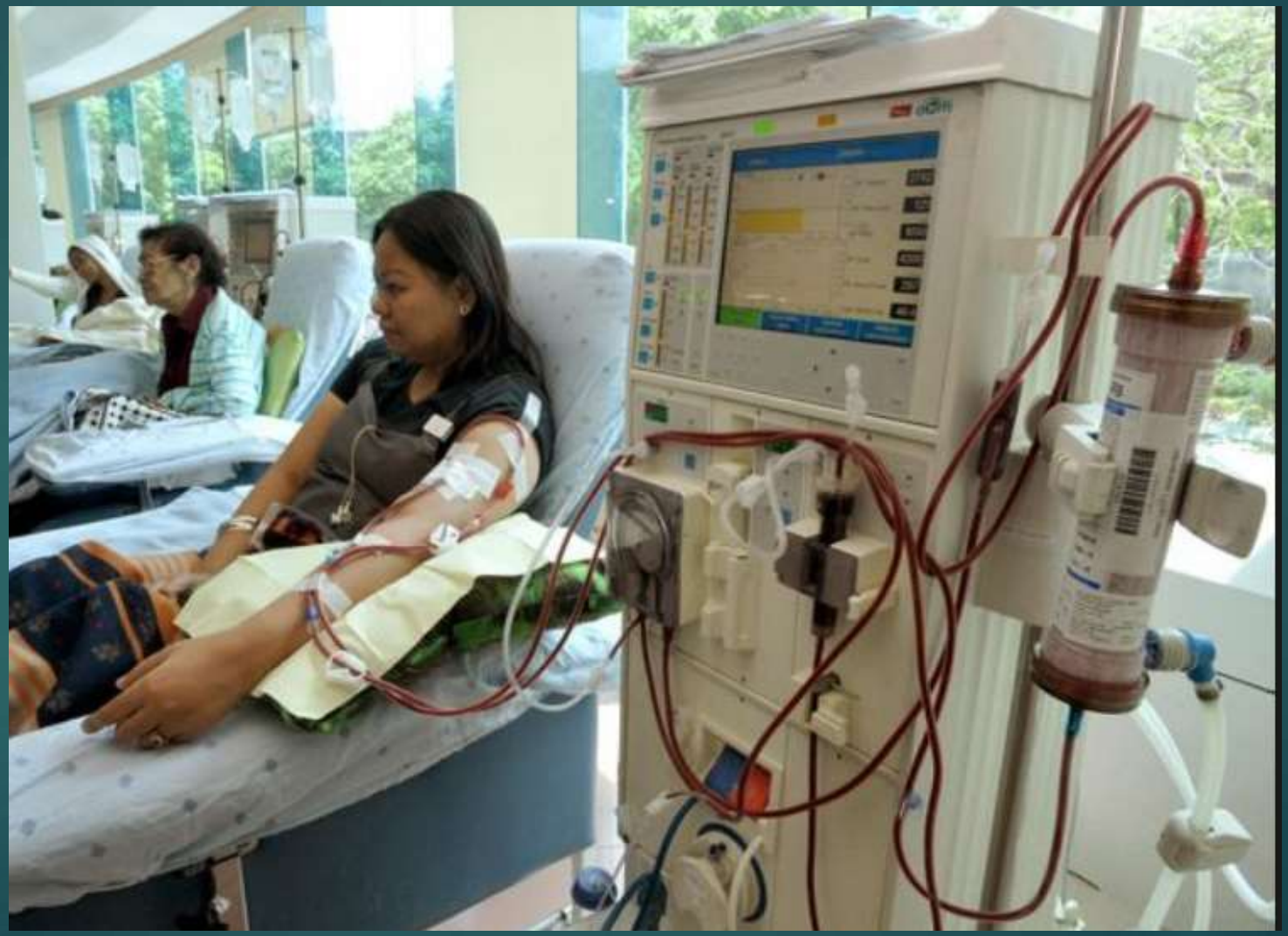
- Cognitive deficits associated with both ESRD and the anemia that accompanies it; also in DM
  - due to deficiency of erythropoietin (hormone secreted by the kidneys that increases the rate of production of red blood cells in response to falling levels of oxygen);
  - 90% of pts
- Cognitive dysfunction, mood disturbance, reduced energy
- Cured by recombinant human erythropoietin

Depression in ESRD

- Depression is the most prevalent psychological problem in the ESRD population (20-50%)

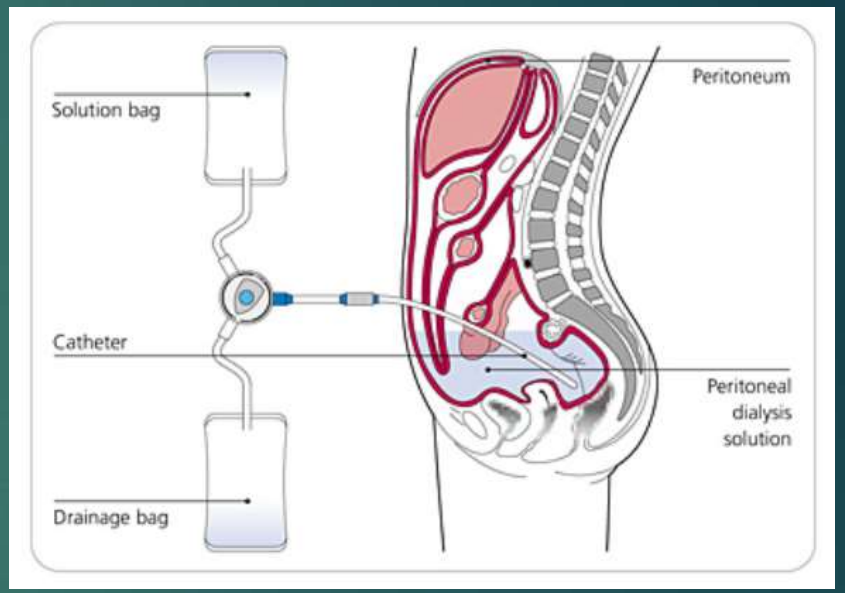
- BDI overestimates depression in ESRD because of somatic symptoms (has been revised)

Hemodialysis



Dialysis

Hemodialysis:
3 days a week and takes
3 to 5 hours a day.



Peritoneal dialysis: catheter – a small plastic tube – that was inserted during an operation is used to introduce dialysis solution into the abdominal cavity. The blood-rich peritoneum is surrounded by the fluid for several hours

Chronic Hemodialysis

- Dialysis Tx successfully reverses many of CNS alterations associated with uremia, but many exhibit impaired learning, memory, and set shifting (but methodological problems in studies)
- Prior to 1990's inadequate studies (lower and inadequate dialysis consequences)
- Well dialyzed pts with ESRD do not manifest significant uremic neurocognitive deficits.
- But these pts commonly have HTN and atherosclerosis.

NP function in Renal Transplantation

- Little research on Transplantation effects
- Effect of lifelong immunosuppressants drugs on neurocognitive function:
  - Neurological complications: tremor, HA, insomnia, ataxia, paresthesias, focal weakness, seizures, blurred vision, MS changes
  - Dose related
  - Glucosteroids: psychosis, emotional lability, severe depression, insomnia, agitation

Neurobehavioral Disturbances and the Pancreas

- Function of Pancreas: Digestion of food and metabolism of carbohydrates; hormone secretion for regulating glucose metabolism; insulin production
- Pancreatic disorders: early severe depression and anxiety
- Pancreatitis: pancreatic encephalopathy & severe pain
- Hyperinsulinism: confusion, slurred speech, motor incoordination

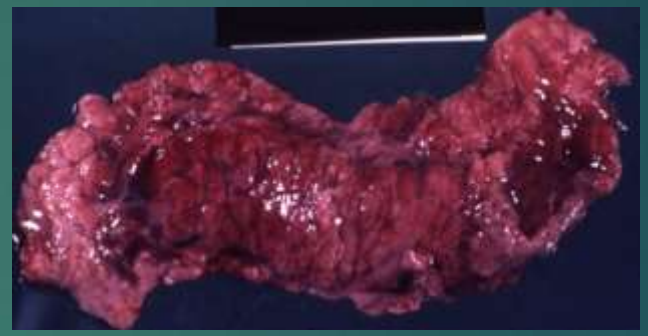
Carcinoma of the Pancreas

- 4th most lethal cancer (after lung, colon, breast); median survival = 4.1 months

- Neuropsychiatric Disturbances (50-75%) :
  - Affective disorder: Depression, anxiety, insomnia, fatigue (before diagnosis)

Pancreatitis

- Inflammation or hemorrhaging of pancreatic tissue; 90% caused by alcohol abuse or biliary tract disease;
  - sx = abdominal pain



- 10-20% of alcoholics
- Pancreatic encephalopathy: delirium, ocular and vestibular abnormalities, cerebellar signs
  - Reversible
  - Chronic relapsing pancreatitis: depression or anxiety, agitation, language and memory disturbances, abnormal EEG

Neuropsychiatric Sxs of Acute Pancreatitis

- 48-72 hours after pain: delirium, ocular & vestibular abnormalities, anxiety, depression
- Only 1 FMRI study: white matter lesions
- Chronic relapsing pancreatitis: depression or anxiety with agitation
- Pancreatic Encephalopathy is rare; electrolyte imbalance
- Death from pancreatitis: encephalomalacia (degeneration or softening of brain tissue after a any form of brain injury) and extensive demyelinization

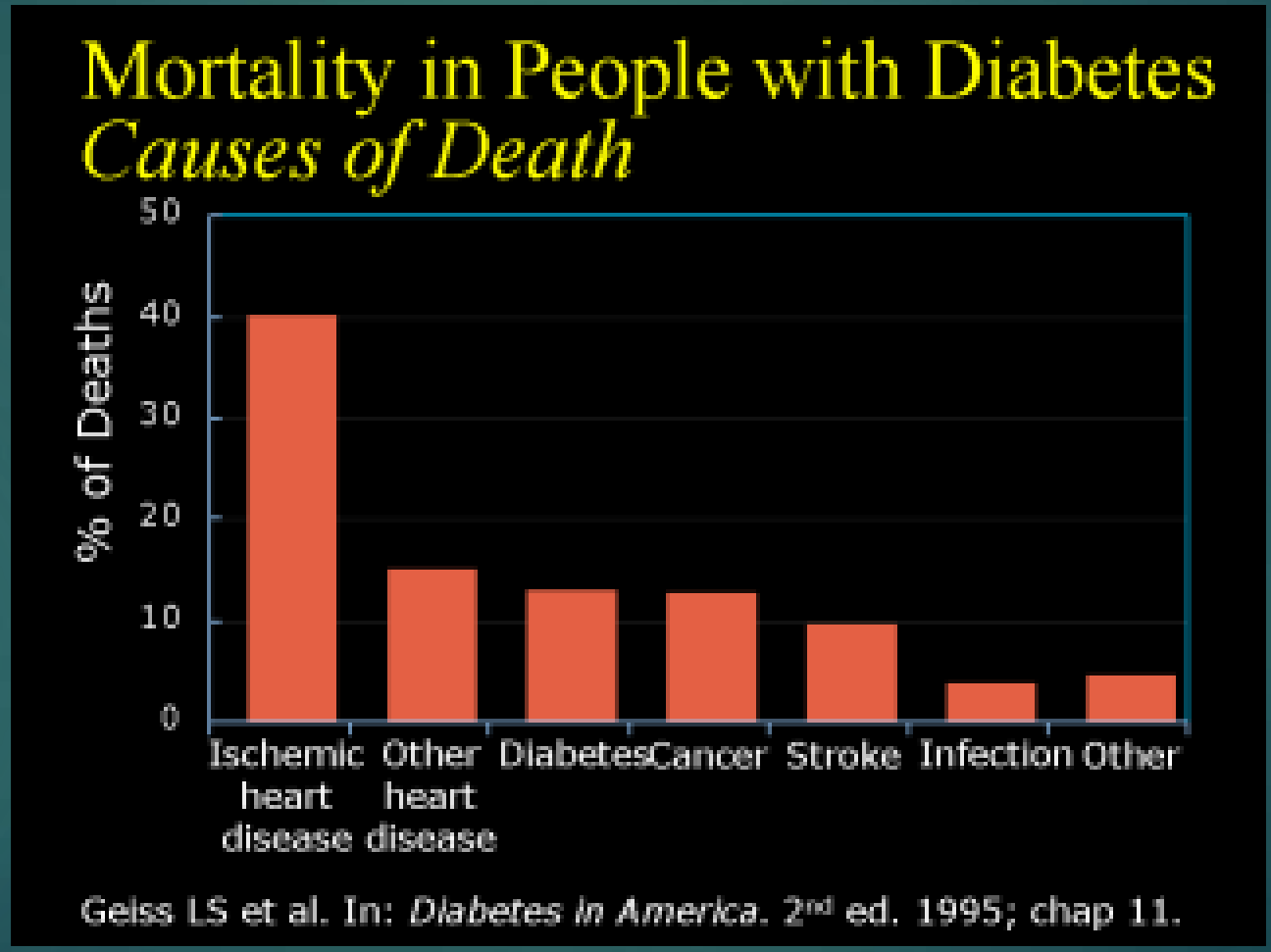
Diabetes-Associated Cognitive Dysfunction

- DM and Cardiovascular disease intertwined

- DM adults have twice the rate of normals of:
  - Hypertension
  - Dyslipidemia
  - Heart disease
  - Stroke

- NP deficits related to DM (independent of CVD)

Diabetes: Ischemic Heart Disease

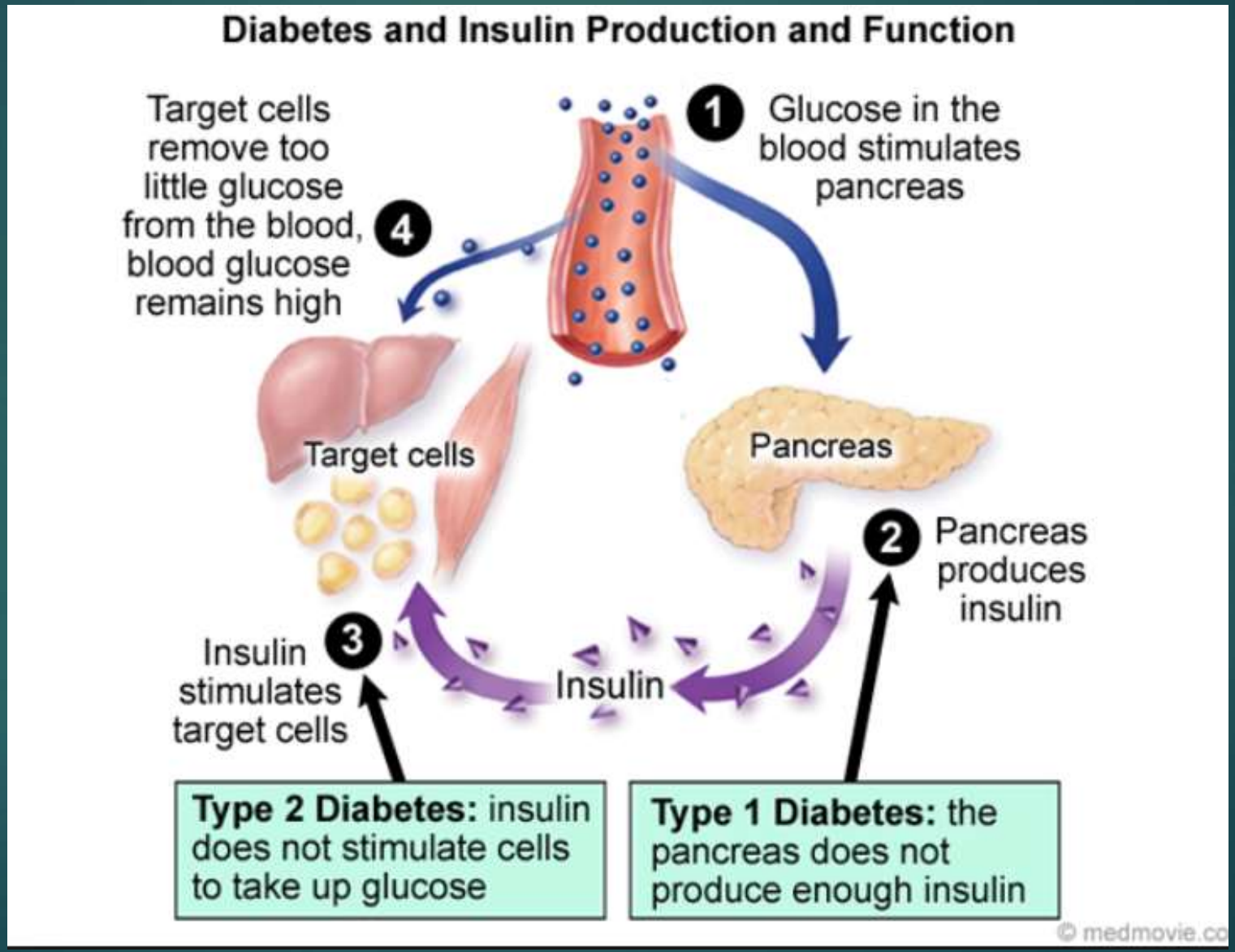


Diabetes Mellitus

- 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

Diabetes and Insulin



Diabetes Mellitus

- Hyperglycemia (high blood glucose levels) is primary issue
- 8 million in US

- DM: Insulin dependent or Type I: inability to secret insulin due to autoimmune destruction of beta cells of pancreas;
  - excessive insulin leads to low glucose level (hypoglycemia); too low, LOC
  - Inadequate insulin leads to hyperglycemia;

    damage to blood vessels, impaired vision, neuropathies

Type 1 DM: child and adolescent

- Onset before age 5 + 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):
  - Attention ↓
  - Memory ↓
  - Visual spatial ↓
  - Executive ↓

Type 1 DM: adult

- 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 ↓

Type II Diabetes

- Non insulin dependent Diabetes: development of insulin resistance, lowered beta cell function; chronic hyperglycemia
- Over 40, and BMI >25
- 90% of all diabetics
- Genetic

Type 2 DM

- Significant Cognitive ↓, esp. Memory , EF, and attention↓
- More likely to have CV disease (but DM effects independent)
- Chronic hyperglycemia as culprit
- Alzheimer's Disease & Diabetes: 2 x risk; The risk is stronger when diabetes occurs at mid-life than in late life; Swedish twin study: developing diabetes before age 65 corresponds to a 125% increased risk for Alzheimer's; esp. EF and PS; Nun Study: its vascular
- People with schizophrenia are at increased risk for type 2 diabetes (before medications)

DM and psychiatric issues

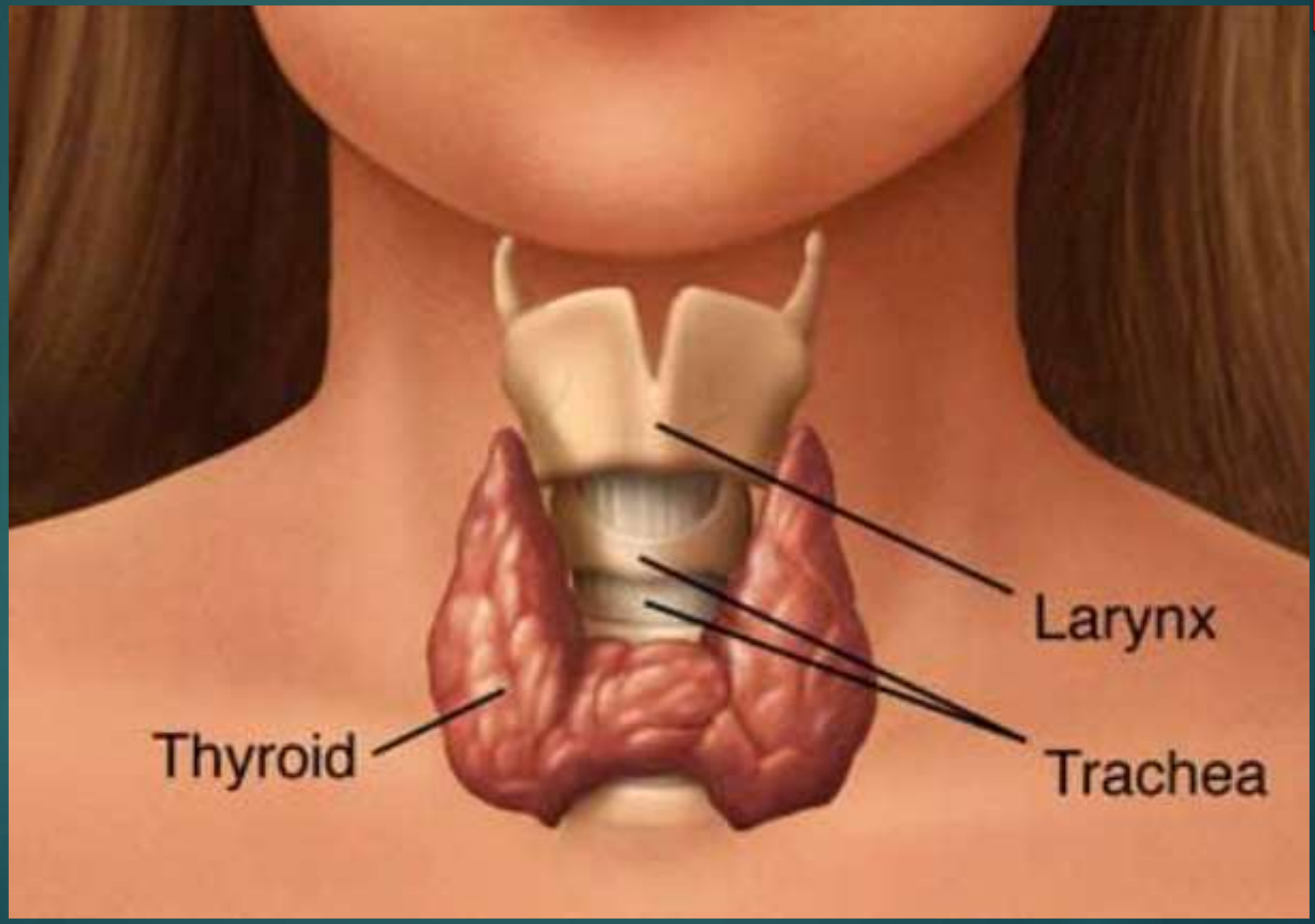
- No significant psychological consequences in children and adolescents

- 8-28% depression in adults (as with chronic disease pts)

DM and poor metabolic control

- Poor control (chronic hyperglycemia) leads to retinopathy, peripheral neuropathy, and cognitive problems
- NP deficits: attention, processing speed, visual spatial processing
- MRI study: 69% had 5 + lesions

Thyroid



Neuropsychology of Thyroid Disorders

- Thyroid: endocrine gland in neck (thyroid and iodine), governed by TSH (Thyroid Stimulating Hormone), stimulation of calorigenesis (oxygen consumption and heat production, protein synthesis)
- Effects depression
- Hypothyroidism: loss or atrophy of thyroid, defective hormone synthesis
- Thyrotoxicosis: excessive thyroid, Graves' disease (nervousness, apprehension, inattention, emotional lability, etc.), Hashimoto's disease (goiter, end in hypothroidism)

Hypothyroidism

- NP deficits: memory, inattention, TMT, Porteus maze, animal naming
- EEG: slowing
- EVP lower, hearing impairment
- Replacement therapy reverses deficits, but not necessarily to normal
- Affect: relation to depression

Hyperthyroidism

- Thyrotoxic effects: slower RT, fatigue, Stroop, memory, Tapping, attention, executive functioning deficits
- NP changes may persist up to 10 years after hyperthyroid episode; correlation with T4 elevation
- EEG: slow rhythm
- Replacement therapy helps, but not perfectly
- Hyperactivity, irritability, fatigue, emotional lability

Old Sperm

- Advanced paternal age is associated with an increased risk of neurodevelopmental disorders such as autism and schizophrenia, as well as with dyslexia and reduced intelligence
- 33,437 singleton children enrolled in the US Collaborative Perinatal Project. At ages 8 months, 4 years, and 7 years tested.
- Bayley scales, Stanford Binet Intelligence Scale, Graham-Ernhart Block Sort Test, Wechsler Intelligence Scale for Children (WISC), and Wide Range Achievement Test

- Advanced paternal age correlated significantly with poorer cognitive scores

Gonadal Steroids and Cognition

- Gonadal hormones (estrogens, progesterones, & androgens) (from ovary and testicles) influence cognition & behavior
- Sexual development: Male or female
- Genetic sexual abnormalities (Turner's, Klinefelter's)
- Testosterone: higher visual spatial ability
- Estrogen decrease: lower memory performance, dendritic spines decrease
- Estrogen increase: decreased visual spatial, better verbal
- Admin. of female hormones to men improves verbal and decreases visualspatial abilities
- Pregnancy: lower working memory

Neuropsychology of Systemic Autoimmune Disorders

- Autoimmune disorders (body's tissues are attacked by its own immune system):
  - Systemic lupus erythematosus (SLE): inflammatory
  - Sjorgen's syndrome: (white blood cells attack moisture-producing glands)
  - Eosinophilia-myalgia syndrome (L-Tryptophan)): fatal flu-like neurological condition (1989 episode: 60,000 ill, 27deaths in contamination)
- Cognitive deficits, but are they psychiatric effects, medication (steroids) effects, or real cognitive deficits

Neuropsychology of Sleep Disorders

- Not sleeping → poor cognitive performance, esp. memory
- Sleep apnea → hypoxia
  - Increased risk for dementia
- REM Behavior Syndrome → Parkinsonism, LBD
- Few studies

Sepsis: Ignaz Semmelweis vs Midwives

- In sepsis, immune system chemicals released into the blood to combat serious infection trigger widespread inflammation. This can lead to low blood pressure, heart weakness, and organ failure
- Older person's risk of cognitive decline increased almost threefold following hospitalization for severe sepsis.
- Severe sepsis was associated with greater risk for the development of at least one new limitation in performing daily activities following hospitalization.

Cancer

- The incidence of cancers of the breast and lung in women, as well as non-Hodgkin lymphoma, melanoma of the skin, and liver in men and women, is rising
- Lung cancer deaths in women continue to rise, though not as effectively as before
- More people are overweight and obese, which increases cancer rates, and physical activity is increasing only slightly
- Cancer treatment spending continues to rise along with total health care spending

Cancers

- Most common: prostate, breast, lung cancer in adults; acute lymphoblastic leukemia and brain tumors in children
- Incidence: 26 per 100T per year in adults; 5 per 100 T in children
- 5 year survival rate for brain tumors: 24% in adults; 75% in children

Cancer of CNS

- 2 Types of CNS cancer:
  - Primary neoplasms of brain & CNS (2 x as common in kids)
  - Metastatic cancers of other organs (twice as common in adults) that can affect CNS functioning either
    - directly (metastases) – 50% from lungs
    - treatment (CNS prophylaxis for childhood leukemia)
- Divided into child and adult versions which can be very different
- Brain tumors develop from abnormal replication of cells due to genetic alterations that evade normal cell regulatory functions & avoid immune system targeting. 99% from glial cells, not neurons

2 types of tumors

- Primary brain tumors
  - Originate in CNS
  - More common in children than adults (Medulloblastoma in kids)
- Metastatic brain tumors
  - Primary cancer outside CNS & spreads to brain
  - They are most common intracranial tumor in adults (4x greater than primary tumors in adults)
  - 20-40% of adults with cancer
  - Most common: lung (50%), breast (15-20%), colon, melanoma (10%)
  - 24-40% of adults with non-CNS tumors develop metastatic brain cancer
  - 80% are in cerebral hemispheres
  - Most common location: gray & white matter junctions

Neuropathology of Cancer

- Marked heterogeneity
- Classification based on cell of origin & proliferative potential
- Benign vs Malignant difference isn't useful in the brain; given importance of brain structures, a "benign" tumor can be lethal. Benign: meningiomas (15% of all brain tumors; peak in middle age; more females (unlike all other brain tumors); malignant: only 2% of all cancer deaths)
- Malignancy in brain tumors references not malignancy but local growth pattern and capacity to spread
- Grading from I to IV based on degree of histological malignancy
- Brain tumors rarely metastasize
- Peak age: 74-84 years of age; average age: 54 y

Grades

Grad	Characteristics	Histologic Type
1	Well differentiated Non-infiltrative; low proliferative potential Slow growing Good possibility of cure with surgery	Pilocytic astrocytoma; meningioma Best prognosis
II	Moderately differentiated Somewhat infiltrative; low proliferative potential Can progress to higher grades	Low grade diffuse astrocytoma Oligodendroglioma
III	Poorly differentiated; brisk mitotic activity Infiltrative Require chemotherapy &/or radiation Progress to higher grade	Anaplastic astrocytoma, etc.
IV	Undifferentiated; widespread infiltration; very mitotically active High degree of necrosis; multimodal TX Rapid recurrence	Glioblastoma Medulloblastoma Choroid plexus carcinoma Worst prognosis; fatal

Incidence rates

- 93% diagnosed in adults
- Most common sites: meninges (34%), lobes of brain (22%; frontal 9%; temporal 7%; parietal 5%; occipital 1%)
- Different types at different ages (1st, 2nd most common)
  - 5-14: astrocytoma, glioma
  - 15-34: pituitary
  - 35-85: meningioma, glioblastoma
- Gender:
  - Higher in women; meningeal tumors 2x higher; pituitary .5 x higher
  - Gliomas higher in males

Mortality

- 5 year survival in 20+ yo: decreases with age, from 64% (in 20s) to 1% in over 80 yo
- Highest proportion of adults with CNS tumors: 60-69yo with 6% 5 year survival rate
- Poorest survival type: *glioblastoma multiforme* in all ages
- Survival with multiple brain metastases is poor (3-6 months)
- Overall survival in children is lowest under 1 year of age
- Risk factors for brain CA: radiation exposure (therapeutic, diagnostic, other); genetics; increase in CNS lymphoma from HIV
- Severity: tumor histology, location, mass affect (herniation)

Presentation and course

- Headaches (most common symptom sx), 35%; due to mass effect
- Signs of increased intracranial pressure (ICP): headaches, nausea
- Seizures (present with szs:15-20% of kids; 25-30% of adults); 40-60% of adults have szs at some time in course
- Progressive neurologic deficits (sensory, motor, ataxia)
- Endocrinopathies
- Cognitive behavioral changes (caused by increased ICP, edema, blood flow obstructions, local effect/focal deficit); often focal
- Most tumors in adults are in cortical locations
- MRI with contrast is imaging of choice; brain biopsy for dx

Risk Factors for Cognitive Deficits

Disease Induced

- Infections
- Pain
- Metastases to CNS
- Disturbances of endocrinologic system

Treatment Induced

- Chemotherapy
- Radiation
- Bone marrow transplantation
- Medications

Treatment

- Three Treatments: surgery, chemotherapy, radiation
- Tx goal of lower grades is “curative”
- For higher grades, Tx goal is palliative, prolong survival.

- Anti-seizure medications and dexamethasone (steroid to reduce swelling)

Surgical Treatment

- Surgery: 1st line TX; curative for meningiomas, low grade tumors
- Brain tumors often associated with hydrocephalus and edema (steroid tx); 10-35% of kids with posterior fossa tumors, shunting used
- Surgical complications: perioperative stroke, motor/sensory deficits, damage to pituitary/hypothalamic areas, posterior fossa or cerebellar mutism syndrome (for months)

Radiation Treatment

- Essential Tx for tumors or metastases; targets rapidly dividing cells; CA cells are replicators, therefore more vulnerable to radiation
- Radiation Tx: can impair normal tissue growth, brain development & function; under 3 most vulnerable; toxicity in very old
- Effects WM tracts (processing speed) and vascular endothelial cells`
- Newer technology: guided 3D conformal delivery; proton beam radiation therapy

Complications of radiation Tx

- Complications:
  - Acute encephalopathy (headache, nausea, drowsiness, fever) within 2 weeks
  - Early-delayed complications (1 to 6 months), associated with reversible demyelination; return to baseline in 12 months; hypersomnia, irritability, headache, attention deficits, memory problems
  - Late-delayed complications (more than 12 months):
    - Adults: not reversible, local radiation necrosis, or diffuse leukoencephalopathy; cognitive deficits from mild to major NCD, vision and/or hearing loss, lower cranial nerve paralysis, radiation-induced tumors; attention & WM deficits common; MRI shows diffuse atrophy, ventricular enlargement, WM abnormalities with severe late encephalopathy
    - Children: NP deficits, neuroendocrine dysfunction; infertility; vascular complications, hearing loss, cataracts, impaired development, secondary malignancy

Mechanisms of chemotherapy induced Cognitive Changes in Cancer

- Direct neurotoxic effects of chemotherapy causing cell injury, altered neurotransmitter levels; effects WM integrity
- Oxidative stress and DNA damage; cell death in subventricular zone
- Induced hormonal changes
- Immune dysregulation and or release of cytokines
- Blood clotting
- Genetic predisposition (DNA repair capability; presence of APOe4)

Chemotherapy

- Cytotoxic chemotherapy agents target rapidly dividing cells;
- High-dose intrathecal chemotherapy and or bone marrow transplant used in very young kids to avoid radiation therapy
- Late effects and complications of chemotherapy (children)
  - WM damage – leukoencephalopathy (esp. with use of methotrexate)
  - Endocrine dysfunction; infertility
  - CV problems
  - Seizures
  - Hearing loss
  - Neuropathies
  - Cerebellar sxs
  - Organ dysfunction
  - NP deficits

All of these things can cause..

- Encephalopathy

- Combination treatments are often implemented which may be more effective in combating the cancer, but poses even greater risks of neurotoxicity for the patient

Effects of Chemotherapy on Cognitive Functioning

- Cognitive dysfunction can appear soon after treatment initiation or as late as 10 years later
- Altered cognitive functioning can be transient or permanent
- Even when cognitive function appears to be in the normal range, low-normal functioning is associated with previous chemotherapy treatment
- Carriers of the Apoe4 allele are at greater risk for reduced neuropsychological performance; when coupled with chemo treatment, their risk substantially increases for cognitive dysfunction

Neurological complications of chemotherapy

- Acute encephalopathy (begins with insomnia, rapidly followed by a state of confusion associated with agitation)
- Stroke-like episodes (characterized by acute onset of encephalopathy with fluctuating motor deficit)
- Chronic encephalopathy – develops progressively for months to years after treatment

Fatigue

- Incidence of fatigue in breast and lung cancer pts: = 99%
- 61% of chemotherapy and radiotherapy pts continue to experience fatigue after Tx stopped
- Reported to last up to 10 years

Incidence and persistence of Cognitive Impairment

- 33% of breast CA pts exhibited NP deficits prior to chemotherapy

- Dysfunction persisted with chemotherapy
  - Baseline = 33% impairment
  - Short term(>3 weeks after Tx) = 61%
  - Long term (1 year after) – 45% stable and 45% improved

Wefel, et al., Cancer, 2004

Breast Cancer & reduced EF: age & education effects

- Women with BC demonstrated significantly reduced activation in the left middle dorsolateral prefrontal cortex and premotor cortex
- Chemotherapy group: reduced left caudal lateral prefrontal cortex activation and increased perseverative errors and reduced processing speed .
- Reduced left caudal lateral prefrontal cortex activation was significantly correlated with higher disease severity and elevated subjective executive dysfunction in the chemotherapy-treated women.
- Negative effects of chemotherapy on brain function may be exacerbated by such factors as increased age and lower educational level.

Chemo vs Radiation

- Cognitive assessment revealed sustained cognitive decline in 11% of HI-CT, 8% of CON-CT, 7% of RT-only patients and 0% in the HC.

- Hypoactivation was found in task-related prefrontal and parietal areas for both CT-groups *versus* RT-only, with HI-CT showing more pronounced hypoactivation than CON-CT, combined with worse task performance. RT-only survivors performed at a similar level to HC while showing hyperactivation in task-related brain areas.

- Long after treatment, CT is associated with cognitive problems and task-related hypoactivation that depend on the specific cytotoxic regimen. This worse performance in patients who received CT could be explained by impaired brain functioning that is more severe with more intense CT. (*JINS*, 2015, *21*, 1–12)

Potential Mediators ?

- There have been some agents identified that might reduce cognitive impairment:
  - Erythropoietin
  - Aspirin
  - Methylphenidate (has demonstrated improvement in children undergoing chemo)

What is Bone Marrow Transplantation (BMT)?

- Used to treat cancers that have not responded well to more standard medical interventions
- Bone marrow transplants involve the destruction of a patient's own bone marrow via chemotherapy and/or radiation therapy, followed by infusion of new cells to generate healthy bone marrow function
- BMT can be classified as allogeneic or autologous:
  - Allo – bone marrow is transferred from a donor
  - Auto – replacement marrow is harvested from the patient, cleaned from disease, and reinfused into patient

BMT patients are at high risk for cognitive deficits

- Most patients undergoing BMT receive chemotherapy or combination chemotherapy/radiation as a preparatory regimen prior to BMT
- Toxicity from high-dose chemotherapy combine with whole-body radiation puts patient at risk for extended hospitalization, posthospitalization recovery, and risk of death from the procedure
- Neurological acute complications are frequent, including transient drowsiness, occasional seizures, or severe encephalopathy; delayed complications typically include mild/moderate cognitive dysfunction with cerebral atrophy.
- Cognitive impairment has been found to persist for months to years following BMT

Research Shows…

- More than 20% of people who receive cranial irradiation suffer significant CNS damage and neurocognitive impairment (Levin, 1999).
- Andrykowski et al., (1992): 56% of their sample of adult BMT candidates scored 1.5 S.D's below the norm on neuropsych battery
- van Dam et al., (1998): High-dose chemotherapy impairs cognitive functioning more than standard-dose chemotherapy on breast cancer patients
- Significant dose escalations of opioids (> or = 30%) cause impaired psychomotor and cognitive functions in cancer patients (Sjogren, 1997).

Research shows..(cont'd.)

- Chemotherapy and radiation therapy have a negative impact on cognitive functioning (Ahles, 1998).
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- In a study by Pereira et al. (1997), 44% of terminal cancer patients had prevalent cognitive impairment upon admission to a palliative care unit. Just prior to death, 62.1% of patients had prevalent cognitive impairment.
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Neuropsych Assessment

- NP assessment postsurgery has been shown to predict survival in adults with malignant gliomas, particularly EF and attention.
- Decline in cognitive function can be early sign of disease progression; improvements in NP function can indicate positive response to Tx.
- NP assessment deferred until after radiation Tx:
  - Before return to work or school

Cancer and Family observations

- Family members are a critical component of follow-up treatment for cancer patients/survivors;
- Cognitive deficits are often more apparent to others rather than the patient themselves. Family members should track the nature and frequency of notable deficits

Cancer & Chemobrain

- 20% and 61% of breast cancer patients who receive standard-dose chemotherapy experience some degree of cognitive dysfunction. Complaints tend to center around short-term memory problems and difficulty recalling words.

- Cognitive deficits caused both by body's inflammatory response to cancer & cancer Tx neurotoxicity

- Cytokines negatively effect brain functioning before CT

NP Assessment of brain tumors

- Adults: cog. Deficits often present before Tx. Deterioration of cog functioning can indicate tumor progression. Cog deficits are often diffuse, often implicating dysfunction in frontal-subcortical pathways. Effects of anxiety and depression must be noted
- Children: NP deficits can be delayed and progressive in survivors, esp. in multimodality Tx. Deficits from mild to severe. IQs post radiation tend to be low average & decline over time is noted. After only surgery, average IQs. Triad effected: attention, WM, processing speed (fluid IQ).

Specific NP domains in cancer

- IQ: preserved in adults, but decline with relapse; children with radiation & CT at early age at risk for IQ decline with increasing time from dx, in range from 2-4 pts per year
- Attention: quite common deficit, esp. sustained attention; WM↓↓, esp. over time in kids
- Processing speed: most common deficit, esp. with radiation tx
- Language: normally ok, but adults can present with aphasia from tumor
- Visualspatial: deficits common in child survivors
- Memory: 3rd ventricle region effect; older child Tx protocols produced more deficits
- Executive Functions: common deficit
- Sensorimotor: depends on tumor location
- Personality: Anxiety & depression common; social skills effected; fatigue issue

POCD: Postoperative Cognitive Decline

- Postoperative Cognitive Dysfunction is independent of type of surgery and anesthetic.
- The incidence of POCD in old and elderly patients at day 7 was higher after CABG surgery than THipJR surgery, but POCD at 3 months was independent of the nature or the type of procedure or anesthetic when comparing Coronary Angiography, THJR, and CABG surgery groups.
- Cardiovascular risk factors were not predictive of POCD after any procedure.

Microbiome

What is the Microbiome?

- The Microbiome is the colony of hundreds of trillions of bacteria and microorganisms which live in the human gut, skin, cells, hair, and body.
- They interact with human cells, enzymes, neurotransmitters and genes.
- Within our bodies resides a dynamic population of gut microbes forming a symbiotic superorganism comprising a myriad of bacteria of approximately 10^{14} cells, containing 100 times the number of genes of the human genome and weighing approximately the same as the human brain. Bacterial cells in the body outnumber human cells by a factor of 10 to 1.
- They have more genetic material than we do.
- The Microbiome is thought to influence our behavior, genetics and illnesses or protection from illness

Microbiome

- Recent investigations indicate that these microbes majorly impact on cognitive function and fundamental behavior patterns, such as social interaction and stress management.

Anxiety and Depression

- Keeping anxiety and depression under control, may improve inflammation in the gut. Treating inflammation in the gut may improve mood by altering brain biochemistry.
- Despite intense interest in how beneficial gut bacteria might promote psychological well-being, few studies have researched these effects in human subjects.
- One study found that a 30 day course of probiotic bacteria (a mix of *Lactobacillus helveticus and Bifidobacteria longum*) led to decreased anxiety and depression.
- Stimulation of the vagus nerve can be an effective treatment for chronic depression that has failed to respond to other treatments

Enteric nervous system: gut feelings

- ENS emerged in the first vertebrates over 500 million years ago
- Second Brain: sheaths of neurons embedded in the walls of the long tube of our gut, or alimentary canal; part of ANS; more neurons here than in PNS; Gut contains 100 million neurons.
- Enteric nervous system uses more than 30 neurotransmitters, just like the brain, and 50% of all dopamine and 95 % of the body's serotonin is found in the bowels
- 90 percent of the fibers in the primary visceral nerve, the vagus, carry information from the gut to the brain and not vice versa

Irritable Bowel Syndrome: Dementia of the gut?

- The idea that irritable bowel syndrome can be caused by the degeneration of neurons in the ENS is lent weight by recent research revealing that 87 out of 100 people with the condition had antibodies in their circulation that were attacking and killing neurons in the gut
- Lewy bodies, also show up in dopamine-producing neurons in the gut. In fact, judging by the distribution of Lewy bodies in people who died of Parkinson's, Braak thinks it actually starts in the gut, as the result of an environmental trigger such as a virus, and then spreads to the brain via the vagus nerve.

AD and Autism and gut

- The characteristic plaques or tangles found in the brains of people with Alzheimer's are present in neurons in their guts too.
- And people with autism are prone to gastrointestinal problems, which are thought to be caused by the same genetic mutation that affects neurons in the brain.

Memory and the Gut

- Gareau *et al.* used a novel object recognition test examining for dorsal hippocampal function and exploration of a T-maze to study GF mice (germ free). These animals displayed an absence of nonspatial and working memory accompanied by decreases in hippocampal BDNF.
- GF mice display significant cognitive deficits. Presence of microbes is crucial for the development of hippocampus-dependent memory.
- The protozoa *Toxoplasma gondii* is known to cause major perturbation to the gut microbiota and is a recognized environmental risk factor for schizophrenia.
- Studies in healthy elderly indicate that latent infection can lead to deficits in goal-directed learning with alterations in dopaminergic neural transmission.