uroContributors (add yourself): Thank you everyone for your work :-).

Week Schedule
MONDAY Lecture: Hemispheric Lateralization
MONDAY Lecture: Age-related Neurodegenerative Disorders
MONDAY Case Discussion: Dementia [quiz]
MONDAY Patient Presentation: Memory Disorders [white coat]
Quiz 5 Online: Noon Monday to Midnight Tuesday

TUESDAY Lecture: Language [8:30am]
TUESDAY Case Discussion: Aging and Loss [quiz]
TUESDAY Review

WEDNESDAY Case Discussion: Childhood Disorders [quiz]
WEDNESDAY Problem Set: Sylvius Challenge II
WEDNESDAY Case Discussion: Cortical Organization and Cortical Deficits
WEDNESDAY Independent Learning: Psych Testing

THURSDAY Lecture: Brain Death and Consciousness Disorders
THURSDAY Case Discussion: Eating Disorders [quiz]
THURSDAY Lecture: Regulation of Body Temperature

THURSDAY Neuro Case Discussions

FRIDAY TBL: Coma and Brain Death [8:30am] [quiz]
FRIDAY Patient Wrap-up

Next Monday: Quiz 6 in-class!

Comments: Write on your OASIS evaluations, email the Evaluation Team, or discuss below.

Why is it that as soon as Ait-Daoud is teaching, the baseline noise/chatter level is 60% louder? Probably a number of reasons. They've made her classes mandatory but the majority of students gain nothing from what she has to say because the material is intuitively obvious or very lite. If you put a hundred people into a room for 50 minutes to work on a teaching activity that is useless, then people are bound to start talking to each other. You could say that we aren't being professional (we are students, not professionals, I am tired of this term being thrown around as a threat by the administration), but I would argue that the administration is partly to blame for wasting our time. seconded. Oh I agree, but that's probably the 'reason'. But professionalism aside, its common respect to dr. ait-daoud and other students to not talk.

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Hemispheric Lateralization
Kathleen Fuchs, PhD
Monday May 2, 2011 8:10 -9:00 am

There is a ppt posted to the course website.

1. Identify which gender has less functional brain asymmetry. Identify whether right-handers or lefthanders have less functional brain asymmetry.
- Left-handers and females have less functional asymmetry

2. Explain two reasons why lateralization of brain function is assessed in advance of brain surgery.
Need info about the functional ability of the involved and spared tissue
- Lateralization of language
    - Extent of surgery minimized in language-dominant hemisphere
- Adequacy of hippocampal structures to support memory consolidation
    - Avoid causing dense anterograde amnesia

3. Describe how the Wada test is performed and interpreted. Name the typical outcome of the Wada test on motor function. Name the typical outcome of the Wada test on the language dominant and nondominant hemispheres.
Intracarotid Amobarbital Procedure a.k.a. - Wada Test
- Injected sodium amytal into the R then L carotid in 15 psychiatric patients
- Contralateral flaccid hemiparesis [=outcome on motor function]
- Speech disruption/aphasia after L injection
- One pt also had brief speech disruption after R injection
- All remained conscious and responsive
- Used to determine lateralization of speech processes so that surgery could be planned to minimize postoperative aphasia

Wada test - Language
- Recovery of function following language-dominant hemisphere injection
    - Speech, naming, ability to follow complex commands - roughly in this order
    - Generally, recovery of speech is dysphasic (contains errors in speech or comprehension) after a language dominant hemisphere injection. [Wiki]
- In nondominant hemisphere, transient mutism followed by an equally intact return of all language functions.

A super-old but still helpful video of Wada Test (with the real Dr. Wada!)

4. State the degree to which speech is lateralized in right-handers.
Speech Lateralization

Montreal Series	Left	Bilateral	Right
Right Handers	96%	0%	4%
Left Handers	70%	15%	15%
Lateralized seizure focus	90%	5%	5%

Can someone clarify what exactly "lateralized seizure focus" means? I'm thinking the person was asking more about "what the lateralized seizure group is" than "what exactly is a lateralized seizure". Anyway, that group is a group of people with seizures that are lateralized to one side of the brain or the other. In the group of patients with lateralized seizures, 90% of them have speech lateralized to the left side, 5% bilaterally, and 5% lateralized to the right.

5. Describe the memory deficits in patient HM who underwent bilateral temporal lobe surgery.
- Severe epilepsy without a clearly localized epileptic focus

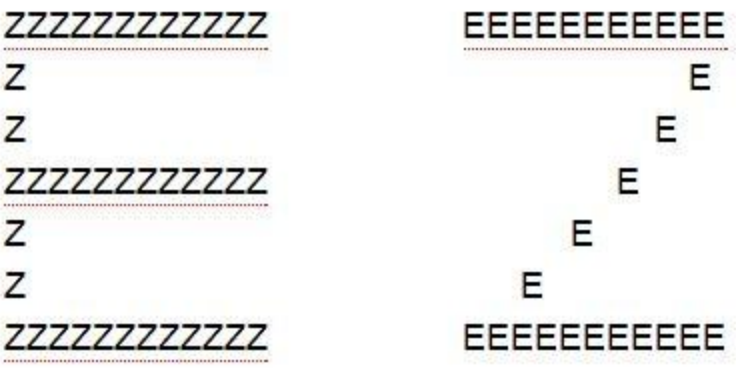
- Bilateral temporal excisions
- Dense anterograde memory deficit
- Normal intellectual functioning

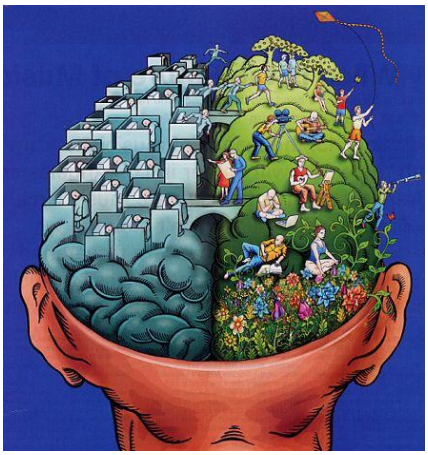
6. Describe the procedure for IAP (Intracarotid Amobarbital Procedure, Wada Test) memory testing. Explain how this test dissociates for anomia and amnesia.

- Patient is presented with several different items (e.g. a plastic piece of pizza, a watch) during period of drug effect in the Wada test
- Patient's recall and recognition is then tested after recovery
    - The doctor asks the patient "can you recall the items you saw?" and they can recall a few or possibly none of the items, but when they are shown the items, they can recognize them better than if they hadn't seen them at all
        - This allows for dissociation of anomia and amnesia
    - This suggests the areas for recognition and recall (memory consolidation; the amnesia pathway) are different
    - **This also tells which side of your brain has better memory function in order to avoid causing the person dense anterograde amnesia (part 2, LO #2)**

7. Distinguish between the two hemispheres in terms of which primarily codes for each of the following: words, shapes, faces, letters, familiar material, novel material.

Left hemisphere - words, letters, familiar material
Right hemisphere - shapes, faces, novel material





When flashed on a scree n into the R visual field (L hemisphere) you see the details of the smaller letter that make up the larger letter, when the image is flashed in the L visual field (R hemisphere) you see the larger letters, or the bigger picture

Left Hemisphere	**Right Hemisphere**
Linear processing (e.g., verbal statements)	Configurational processing (e.g., faces)
Familiar material	Novel information
Detail (local)	Whole (global)
Contralateral attention	Contralateral AND Ipsilateral attention (??)

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Age related neurodegenerative disorders
David Bourne MD
Monday May 2, 2011 9:10-10:00 am

Handout and ppt posted to course website.

1. Describe two ways to classify neurodegenerative diseases / movement disorders

- Clinical "sign/symptom"-based classification
  - Dementias (Cortical Degeneration): AD, DLB, FTLD, CJD
  - Movement Disorders
    - Further subdivided into akinetic/rigid (Parkinson's), hyperkinetic syndromes (Huntington's), cerebellar ataxia (inherited or sporadic), diseases of motor systems (ALS)
  - Autonomic Failure
- Pathologic "proteinopathy"-based classification (e.g. beta-amyloid and tau, vs. alpha-synuclein)
  - β-Amyloid and Tau (Alzheimer's)
  - Tau (FTLD)
  - TDP-43 (some FTLDs)
  - Alpha-Synuclein (make up Lewy bodies in Parkinson's & DLB)
  - Trinucleotide Repeats (CAG seen in Huntington's)
  - Motor Neuron Diseases (ALS)
  - Prions (CJD)

2. Identify the key pathologic findings in Alzheimer's disease and describe underlying pathogenetic associations in this disorder

· Clinical features: dementia + motor dysfunction, language difficulty, and loss of mathematical skills; key feature: no fluctuation in severity of symptoms; while clinical diagnosis is often correct, neuropathologic assessment of brain tissue is useful to confirm clinical diagnosis

· Gross findings: cortical & hippocampal atrophy (with sparing of occipital lobe & motor cortex); **hydrocephalus ex vacuo**; normal substantia nigra pigmentation

· Key microscopic findings: b amyloid plaques, NF tangles, granulovacuolar degeneration, Hirano bodies, amyloid deposition in arteries & arterioles; tangles, in particular, show pattern of spread throughout brain that correlates most closely with clinical disease severity (rather than density of plaques)

o b-amyloid plaques**:** dense core; can stain with silver or with anti-tau or anti-b4 antibody stain; amyloid deposition w/ other protein constituents, including tau

o Tangle: is intra-neuronal; consists of hyperphosphorylated tau protein aggregates

3. Identify the key microscopic findings in Lewy body dementia and recognize important clinical findings in this disease

- Clinically: **Fluctuation in cognition, recurrent visual hallucinations, motor feature of parkinsonism** (2/3 required for diagnosis)
- Pallor of substantia nigra and locus ceruleus, mild to moderate cortical atrophy
- Key microscopic feature is the **cortical Lewy Body** - alpha-synuclein positive (cortical lewy bodies are NOT present in idiopathic Parkinson's disease--instead have Lewy bodies only in the substantia nigra)
  - other microscopic findings include plaques (diffuse and neuritic), Lewy-related neurites, and cortical microvacuolization

4. Identify the key gross and microscopic findings in frontotemporal dementia and recognize important clinical findings in this disease

- preferentially affect frontal and temporal lobes and subcortical white matter
- FTLDs show abnormal accumulation of tau protein in neurons and/or glia
- gross findings: variable degrees of atrophy involving frontotemporal regions

- microscopically: cortical microvacuolization and gliosis. **NO AB DEPOSITS** as seen in AD
- Clinically: predominance of deterioration in personality and social function. patients may neglect social hygiene, exhibit impaired judgement, disinhibition, and stereotyped behavior. If memory deficits appear, they usually appear later in the course of illness.
- Pick's disease: severe "knife-edge" atrophy

5. Identify the key microscopic findings in Creutzfeldt-Jacob disease (including vCJD) and describe unique properties of prions

- Prion
    - Proteinacous infectious particle
    - Normal prion protein, PrP^{c}, has an alpha-helical internal structure, which is replaced by a beta-pleated sheet structure, in the "diseased" configuration, PrP^{Sc}.
    - It is thought that PrPc is converted to PrPSc through a protein-protein interaction, a process by which the abnormal protein somehow acts as a template upon which the previously normal conformation of the protein is altered
    - Prions are highly resistant to standard chemical, thermal, enzymatic, and radiation-based degradation techniques
    - Able to transmit spongiform disease without a nucleic acid intermediate
- Affected Pts are usually in their 7th decade and present with rapidly progressive dementia, myoclonus, ataxia, visual disturbances, and pyramidal/extrapyramidal signs, and the average pt survives about 4-6 mo.
- 14-3-3 protein, sensitive but not specific to CJD (found in more than 90% of patients' CSF)
- Key microscopic features include: **neuronal loss, gliosis and "spongiform" change of grey matter**
- Grossly appears normal, however microscopically looks like a sponge (may show cerebral cortical and/or cerebellar atrophy w/ spongiosus); affects grey matter more than white matter
- PrP subtyping seen in CJD on Western Blot shows nonglycosylated proteins (19 and 21 kDa)
- vCJD - cerebellar **plaques** & spongiosus
    - *vCJD is the prion disease linked to bovine spongiform encephalopathy (BSE) (aka "mad cow disease"); vCJD affects younger patients, there is a longer duration of illness, and patients typically lack the characteristic EEG findings of sporadic CJD.*
- Sporadic fatal insomnia refer to a variant of sporadic CJD with progressive thalamic and hypothalamic dysfunction

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Dementia
Bruce Cohen, MD
Monday May 2, 2011, 10:10-11AM

Required: Dementia Handout (posted on course web site). "I've made this the primary reference since research in dementia is a rapidly developing field and the information on the handout is more up-to-date than the textbook. However, with regard to discussion and explanation of various points, the textbook still does explain things in more detail, and therefore is listed as an additional reference."

Optional for additional explanation: Theory and Practice of Psychiatry. Chapter 6: Dementia pp 115-135

1) List the key aspects of the clinical syndrome of dementia and how it differs from other psychiatric conditions (particularly delirium, mood disorders, and schizophrenia)

- **Dementia**: A global decline in cognition from a previous level (memory impairment plus at least one other cognitive symptom) in clear consciousness
    - in contrast to delirium, which is an acute decline in cognition commonly associated with an altered level of consciousness

2) Define mild cognitive impairment and amnestic disorder. Describe how you would distinguish a case of dementia from a case of mild cognitive impairment (MCI) or a case of amnestic disorder

- **Mild Cognitive Impairment**: Mild memory problems
    - More circumscribed than dementia
    - Was formerly considered a "normal part of aging", but is no longer
        - perhaps a transitional stage of evolving Alzheimer's
            - Neurofibrillary tangles in medial temporal lobe, diffuse amyloid in neocortex
    - Characterized by problems finding words (on "tip of tongue")
        - Patient typically is aware of his/her MCI and worried about it
- **Amnestic Syndrome**: More severe memory problems but extent of cognitive impairment still is limited to ability to consolidate short-term memories into long-term memories
    - DSM-IV diagnostic criteria
        - A. The development of **memory impairment** (impairment in the ability to **learn** new information **or** the inability to **recall** previously learned information).
        - B. The memory disturbance causes **significant impairment** in social or occupational functioning **and** represents a **significant decline from a previous level of functioning**.
        - C. The memory disturbance does **not** occur exclusively during the course of a **delirium** or a **dementia**.
        - D. evidence of direct physiological consequence of a general medical condition

3) List the overall goals of assessment and treatment of the patient with dementia

- Establish the clinical diagnosis of dementia
- Determine the cause of the dementia
- Establish a treatment plan
    - Symptomatic and behavioral management
        - Depression, wandering, agitation, severe anxiety, sleep disturbance, "catastrophic reactions"
    - Family education and support
    - Treatment of comorbid conditions
        - Medical: Urinary tract infection, heart failure, medications
        - Psychiatric: Delirium, Depression
    - Primary prevention or treatments to slow progression of cognitive problems

4) Describe the clinical presentation of dementia due to Alzheimer's disease and how it differs from that of dementia due to vascular disease, Parkinson's Disease, Lewy-Body Disease, Pick's Disease, and Huntington's Disease

- **Alzheimer's Disease**
  - the most common etiology of dementia (50-60% of cases)
  - Can only be diagnosed definitively on autopsy or brain biopsy
  - Criteria for Diagnosis
    - Multiple cognitive deficits with both:
      - **Memory impairment** (impaired ability to learn new information or to recall previously learned information)
      - **One or more** of the following cognitive disturbances
        - **Aphasia** (language disturbance)
        - **Apraxia** (impaired ability to carry out motor activities despite intact motor function)
        - **Agnosia** (failure to recognize/identify objects despite intact sensory function)
        - **Executive function impaired** (planning, organizing, sequencing, abstracting)
    - Decline from previous level of functioning, with significant impairment
    - Course: **Gradual onset** with continuing cognitive decline
    - Cognitive defects are not due to
      - Other CNS conditions: Cerebrovascular disease, Parkinson's disease, Huntington's Disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor
      - Systemic conditions known to cause dementia (hypothyroidism, vitamin B or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV)
      - Substance-induced conditions
    - Deficits not exclusively during delirium
    - Not better accounted for by another Axis I disorder (MDD, Schizophrenia)
  - Pathology
    - Bilateral and symmetrical neuronal loss with cortical atrophy
    - Primarily affects temporal-parietal neocortex and hippocampus
      - Frontal lobes less intensely involved
      - Primary motor, sensory, and visual cortex relatively spared
      - Less subcortical involvement
    - **Amyloid Plaques**
      - Extracellular lesions with core of beta-amyloid surrounded by dystrophic neuritic processes
    - **Neurofibrillary Tangles**
      - Intracellular lesions made up of abnormally phosphorylated microtubules and tau protein
    - Other associated findings:
      - Granulovacuolar degeneration
      - Hirano bodies
      - Microvascular amyloid angiopathy

- **Vascular Disease**
  - Caused by **one or more strokes** (documented by history, focal neurological signs and symptoms, imaging studies)
  - Course: **Abrupt** followed by a **stepwise decline in cognition** with successive episodes of vascular insult (AD is more insidious)
  - Pattern of cognitive deficits is "patchy," depending on which regions of the brain have been injured (could include cortical features, subcortical features, or both)
  - Associated focal neurological signs and symptoms may be present (Babinski, pseudobulbar palsy, gait abnormalities, exaggeration of deep tendon reflexes, extremity weakness)
  - Imaging reveals multiple vascular lesions involving the cerebral cortex and subcortical structures
    - Many nondemented elderly people also demonstrate cortical atrophy, enlarged ventricles, and ischemic changes so it cannot be diagnosed from imaging alone
  - Onset may occur at any time in late life but its incidence declines after 75 (incidence of AD continues to rise)
  - High comorbidity between Alzheimer's Disease and vascular dementia (may be superimposed or vascular dementia can serve as a risk factor for the development of AD- probably because the vascular disease **impairs the ability of the brain to flush amyloid from the brain as effectively**)
    - Generally only one diagnosis is made during the person's lifetime (both are often found on autopsy)

- **Parkinson's Disease**
    - Dementia occurs in 20-60% of PD patients, particularly later in the illness
    - Dementia has an insidious onset with predominately subcortical features
    - Some patients are actually found to have had findings consistent with comorbid AD or Lewy Body Disease post-mortem
    - Treatment can be complicated and difficult
        - Especially sensitive to deliriogenic effects of antiparkinsonian psychotropic drugs
            - Anticholinergics cause worsened dementia and/or delirium
            - Dopaminergic drugs (apomorphine, ropinirole, pramipexole, etc) can cause delirium or psychosis
        - Antipsychotic drugs prescribed to treat delusions or agitation can lead to worsening of the patient's parkinsonian stiffness, tremor, bradykinesia, and postural instability
        - Parkinson's Disease predisposes to major depressive disorder, which in itself can impair cognitive function
- **Lewy Body Disease**
    - Resembles AD clinically but **tends to progress more rapidly** and to be associated with parkinsonism and **prominent visual hallucinations**
    - May account for up to 25% of cases of dementia
    - On autopsy, in addition to features of AD, one sees Lewy inclusion bodies in the cerebral cortex
    - As in the case of patients with Parkinson's disease, these patients may be particularly difficult to treat given both their prominent psychotic symptoms and their increased sensitivity to the extrapyramidal side effects of antipsychotic medications due to preexisting Parkinsonism
- **Pick's Disease**
    - Often mistaken for AD
    - Preferentially affects the **frontal and temporal lobes** (symptoms contrast those seen in AD)
        - Initial signs to involve **more "hypofrontal" changes in personality and cognition** (apathy, behavioral disinhibition, prominent language abnormalities)
        - Memory problems and apraxia tend to develop later in the course of the illness
    - Neuroimaging typically reveals prominent frontal and/or temporal atrophy, with relative sparing of the parietal and occipital lobes
    - Diagnosis of Pick's Disease can only be confirmed by the autopsy finding of **Pick inclusion bodies** (Pick's disease is one of a family of so-called "frontotemporal dementias," the others of which don't demonstrate Pick bodies)
    - Can't be definitively distinguished from atypical AD at the bedside
    - Typically has onset between 50 and 60, though it sometimes occurs in older individuals
    - Treatment is the same as for AD, though it may be required earlier in the course of illness for psychiatric and behavioral disturbances
- **Huntington's Disease**
    - Autosomal dominant condition (50% likelihood of inheritance, regardless of sex, should also have one affected parent)
    - Usually has onset in late 30s, early 40s
    - Presents with insidious onset of subcortical dementia with the earliest symptoms being nonspecific emotional ones (depression, anxiety, irritability), followed by personality changes (apathy, irritability), executive dysfunction, memory impairment, along with progressive choreiform disorder
        - clinical triad: depression, chorea, executive dysfunction
    - Early structural neuroimaging is unremarkable.
        - PET scans early in the disease may show ***hypo***metabolism in the caudate and putamen.
            - As the disease progresses, the caudate atrophies, leading to characteristic enlarged and squared-off lateral ventricles on structural brain imaging
    - Clinical diagnosis has traditionally been based on the patient having characteristic symptoms in the context of a positive family history; single genetic mutation on chromosome 4 responsible for Huntington's disease was identified in 1994 (genetic test now available)
    - Genetic aberration is not a point mutation but a string: too many CAG repeats, leads to instability of the gene's protein product (huntingtin)
    - **Anticipation**: Mutation is amplified by the addition of more repeat sequences as it is passed down to subsequent generations
    - Mechanism of neurotoxicity is still unclear

- As with other neurodegenerative disorders, it may somehow trigger excessive excitotoxicity or apoptosis in the basal ganglia and ultimately the cortex
- Inevitably fatal within 10-15 years of diagnosis
- Primary treatment strategy is to manage the dyskinesia with **dopamine receptor antagonists** and to address secondary psychiatric syndromes through pharmacotherapy, counseling, and behavioral interventions

5) Describe how Alzheimer's disease evolves as it moves from early to middle to late stages of the disease

- Onset is usually after age 55
- Steady decline in cognition (2-3 points on Mini-mental per year)
- Survival rates are variable- mean is 8 years after diagnosis (range of 1-14 years)
- At first, long-term memory is intact but short-term impaired; social graces preserved
- Common psychiatric complications
    - Depression can be early symptom: Demoralization vs. MDD
    - Can develop delusions
    - Wandering, agitation, severe anxiety, sleep disturbance, "catastrophic reactions"

Alzheimer's Disease

	Stage 1	Stage 2	Stage 3
Duration of Illness	1-3 years	2-10 years	8-12 years
Memory	Impaired short-term	Impaired short- and long-term	Severe impairment
Visuospatial Skills	Poor complex constructions and geographic orientation	Poor simple constructions and spatial orientation	Severe impairment
Language	Anomia; poor verbal fluency	Fluent aphasia	Severe impairment
Other		Acalculia; ideomotor apraxia	Urinary and fecal incontinence
Personality changes	Indifference; irritability	Indifference; irritability	Severe impairment
Psychiatric symptoms	Possible delusions	Possible delusions	Severe impairment
Neurologic Exam	Normal	Aberrant motor behavior (pacing, restlessness)	Limb rigidity; flexion posture
EEG	Normal	Background slowing	Diffuse slowing
CT/MRI	Normal	Normal or mild atrophy/ ventricular enlargement	Ventricular Dilatation and sulcal enlargement
PET/SPECT	Bilateral posterior parietal-temporal hypometabolism/ Hypoperfusion	Biparietal and frontal hypometabolism/ hypoperfusion	Biparietal and frontal hypometabolism/ hypoperfusion

if you can stand my highlights, here is a clearer image (the last one was really blurry) Thanks!

6) Describe what you might see in neuroimaging of a patient that you are assessing for possible Alzheimer's disease and how functional neuroimaging (PET, SPECT, fMRI) reveals abnormalities earlier in the course of illness than anatomic neuroimaging (CT/MRI)

- CT/MRI
    - **Greater atrophy than typically seen** (statistical finding)
        - Normal elderly brain can show marked atrophy and in early Alzheimer's some patients have little atrophy
    - Important to rule out other causes of dementia (tumor, vascular, subdural hematoma, hydrocephalus)
- Functional Imaging: Often precedes anatomic changes
    - PET
        - Early on, at rest, extensive **hypometabolism** of glucose in **temporal-parietal neocortex**
        - Later, hypometabolism in frontal cortex (primary motor, sensory, visual cortices spared)
    - SPECT
        - Early on, mild **global decreases in cerebral blood flow (CBF),** with more marked decreases in the

temporal-parietal cortex
        - Later on, overall CBF declines further and frontal lobes show more extensive hypoperfusion
            - CAVEAT: Temporal-parietal hypoperfusion **not specific to Alzheimer's** (also seen with sleep apnea, hypoxic brain injury, vascular dementia)
    - "Activation" PET and fMRI
        - Images obtained during a mental task that requires verbal memory that are then compared to baseline images obtained at rest
        - Young, asymptomatic individuals at higher risk for dementia (carriers of apoE4) showed increased activity in the hippocampal and parahippocampal areas
            - Suggests that presymptomatic individuals need to use more brain resources than do control subjects in order to perform the same tasks
        - Individuals who demonstrated this finding were more likely to show cognitive decline when tested two years later
        - It's likely that as these compensatory mechanisms begin to fail, a pattern of hypoperfusion comes to predominate
    - Because of their expense and availability, functional imaging studies are used only at academic centers for research purposes (findings also contribute little to diagnostic process since DSM-IV criteria are relatively sensitive; may offer some incremental benefit in a small subset of cases where the presentation is ambiguous)

7) Describe the major known risk factors for Alzheimer's (age, genetics, including the role of ApoE4, traumatic brain injury, vascular disease) and why it's possible that these factors contribute to developing Alzheimer's disease.

- Age
    - Perhaps the most important risk factor
- Genetics
    - About **5%** of cases are familial with autosomal dominant transmission (the rest are sporadic)
    - Only 40% concordance in monozygotic twins, the same for dizygotic twins and so environmental factors/exposures must also play a role
    - ApoE4
        - One of 3 alleles for the gene apolipoprotein E
        - 1 copy correlates with 3 times higher risk, 2 copies = 8x greater risk
        - ApoE4 **binds avidly to beta-amyloid** and can be found in plaques, tangles, and amyloid angiopathy
        - Just one risk factor, though, and testing for it is of little value since up to 50% of patients with Alzheimer's Disease are not E4 carriers, and only 30-40% of E4 carriers ultimately develop Alzheimer's Disease
- Traumatic Brain Injury
    - Not clear if causational or just hastens the onset
    - One study found it to only be a risk factor for ApoE4 carriers
- Vascular Disease
    - Can cause a combined dementia (AD + vascular dementia)
    - Likely because it contributes to decreased clearance of amyloid)

8) Describe the major etiologic theories of Alzheimer's disease and also their implications for potential rational therapies (i.e., therapies that don't simply attempt to treat the symptoms of the disease but attempt to remedy the underlying pathology of the disease, thereby preventing the onset of the illness or slowing its progression):

a) Acetylcholine deficiency

- Also, describe the mechanism of action of Donepezil (Aricept), Rivastigmine (Exelon), and galantamine (Reminyl), and describe the controversy over whether it is worth prescribing these drugs (expense, side effects, don't change underlying progression of disease, but may slow)

- Acetylcholine plays a key role in memory
    - Anticholinergic drugs impair memory similar to AD
    - Greatest transmitter loss in AD is acetylcholine
        - Corresponds to loss of neurons in **Nucleus Basalis of Meynert**, which projects throughout the brain

- Analogous to loss of dopamine in Parkinson's Disease
- Treatment Implication = Cholinergic Drugs
  - More effective early in course
  - May not see that they are helping since the patient still shows decline over time but slope of decline is less steep
  - Don't change rate of progression (if you stop taking them you decline to where you'd have without taking them)
- Treatments
  - Tetrahydroamino Acridine (THA) or Tacrine (Cognex)
    - First cholinesterase inhibitor
    - No longer prescribed
  - **Donepezil** (Aricept) and **Rivastigmine** (Exelon)
    - **Cholinesterase inhibitors**
      - decreased ACh degradation
    - Associated with modest benefit in some individuals
    - Can be taken once daily (Aricept) or twice daily (Exelon)
    - Transdermal patch form of rivastigmine has been approved (bypassing the gut improves GI side effects)
    - Not associated with liver toxicity (some patients complain of GI upset and benefit from starting at a lower dose and then titrating upward)
  - **Galantamine** (Reminyl)
    - Most recently approved drug
    - Cholinesterase inhibitor *and* **allosteric modulator of nicotinic receptors** on cholinergic neurons
      - decreased ACh degradation + increased ACh release
- Treatment Implication #3: Muscarinic or nicotinic ACh receptor agonists (none are available at present)

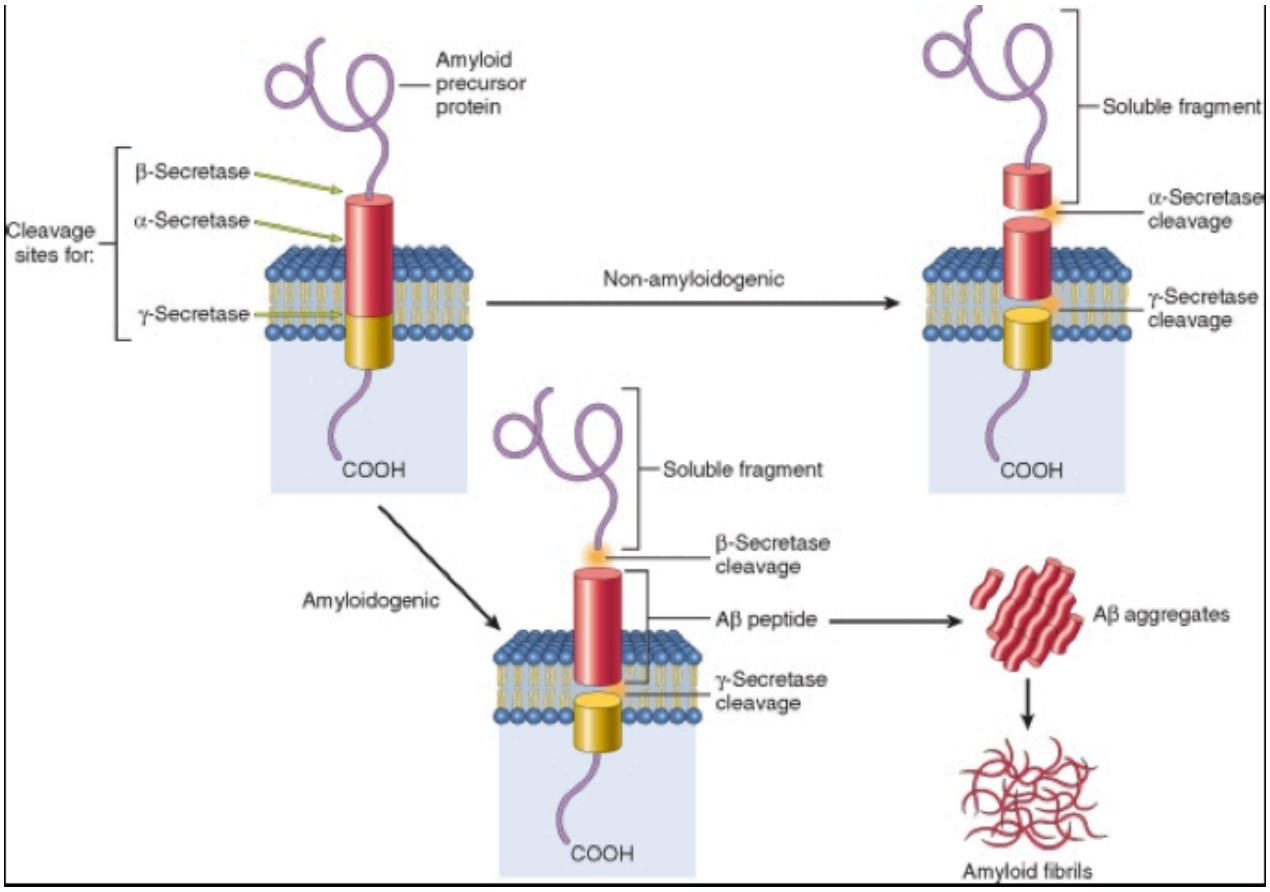
b) Glutamate/Excitotoxicity hypothesis
- Also, describe mechanism of action of memantine (Namenda)
- Describe the hope (so far unrealized) that antioxidant therapy might provide benefit

- Glutamate is an excitatory neurotransmitter
- NMDA receptor for glutamate:
  - Ligand-gated calcium ion channel
  - Others sites on channel for glycine, zinc, polyamine facilitate Ca influx through further allosteric modification
  - Mg and PCP modify the channel to inhibit Ca influx
- Too much glutamate → influx of too much calcium → activation of enzymes that produce free radicals → toxic effect on membranes of neurons and organelles → apoptosis due to excitotoxicity
- Mechanism has been implicated in both acute diseases (stroke) and chronic neurodegenerative diseases (Parkinson's, Huntington's, ALS) and so may play a role in Alzheimer's Disease as well
- **Treatment** Implication #1: **Glutamate Blockade**
  - **Memantine** (Namenda): **NMDA-receptor antagonist** (blocks excessive activation by glutamate)
    - Can be used either alone or combined with cholinesterase inhibitors
    - Small clinical benefit but generally well tolerated
      - Most common side effects: dizziness (7%), headache, constipation (6%)- tend to be mild and transient
    - Approved for moderate to severe AD (studies for early stages are in progress)
- **Treatment** Implication #2: **Antioxidant Therapy**
  - Vitamin E: Inexpensive, few side effects
  - L-Deprenyl or selegiline (Eldepryl): Irreversible selective inhibitor of MAO-B (do inhibit MAO-A at higher doses)
    - Offered no benefit with regard to cognitive decline in moderate AD patients compared to placebo
    - Functional decline was delayed by about 7 months
      - functional decline ~ need for institutionalization or death
    - Combination of both drugs was worse than using either alone
  - In a study of MCI patients, Vitamin E did not show any slowing of progression to AD (its reputation has declined since initial study)

- taking supplements is **no longer recommended due to slightly higher mortality and heart failure**, particularly associated with taking high dosages

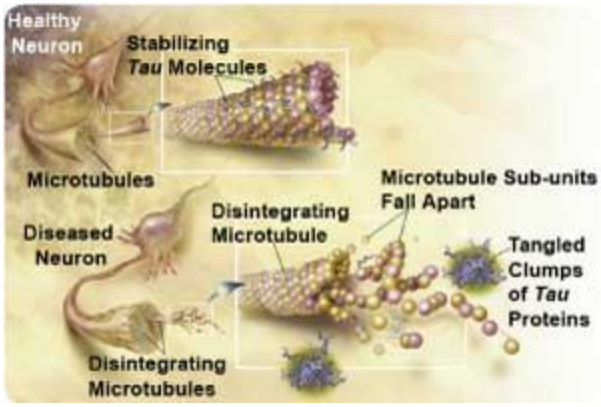
c) Amyloid Cascade hypothesis

- Question: Are the plaques and tangles responsible for the degeneration of brain neurons or are they simply markers of where neuronal death already has occurred? (most researchers believe the former)
- Amyloid cascade hypothesis suggests that amyloid-beta and tau both cause the destruction of neurons, with Aβ initiating the cascade of destruction
    - Aβ is a short peptide fragment that is derived from Amyloid Precursor Protein (APP) (gene for APP is on chromosome 21)
    - APP sticks through the neuronal cell membrane: one part of the protein is inside the cell and another part outside (both are hydrophilic; transmembrane part is hydrophobic)
        - Two proteases (beta-secretase and gamma-secretase) carve out Aβ from APP
            - Process occurs in virtually all cells in the body
            - First beta-secretase cuts at the portion outside of the cell
            - Gamma-secretase cuts APP within the cell membrane itself
                - Two major genes for gamma-secretase complex are presenilin-1 and presenilin-2



    - Physiological purpose of APP isn't clear, but it appears that APP fragments are involved in the regulation of various cellular activities such as axonal transport, cell adhesion, cholesterol metabolism, gene transcription, and cognitive process (may have neurotrophic and/or neurotoxic effects)
    - Production of APP fragments is probably regulated by whether or not secretases are allowed access to APP substrate (controlled by binding of other proteins to APP: C-terminal binding substrates, APOE, various cytokines)
    - When Aβ is released into the aqueous environment outside the membrane, the hydrophobic regions cling to one another, forming soluble assemblies --> formation of **amyloid** (consists of Aβ core surrounded by coating of neuronal fragments)
    - Both free-floating, soluble Aβ as well as insoluble Aβ clusters seem to disrupt neuronal function, ultimately leading to cell death (Aβ may change the cellular activity of kinases that phosphorylate tau proteins, leading to hyperphosphorylation of tau proteins)

- **Tau Protein**
  - Small, highly soluble microtubule-associated proteins
  - Exist primarily in neurons
  - Interact with tubulin to **promote tubulin's assembly into microtubules** (act to stabilize microtubules)
  - Microtubules form neuronal cytoskeleton, providing structural support and tracks for movement of organelles and others structures within the neuron



- Tau is regulated by several different kinases, which phosphorylate tau, thereby modifying its shape and activity
- **Hyperphosphorylation of tau** (perhaps due to excess Aβ) leads to tau misfolding, converting it from a highly soluble protein into an extremely insoluble protein → aggregates of twisted microfilaments (neurofibrillary tangles)
- Altered tau proteins kill the neurons, perhaps by disrupting microtubules
- Familial Alzheimer's
  - It is likely that Aβ initiates excessive phosphorylation, leading to misfolding of tau
  - However, mutations in the tau gene itself also generate neurofibrillary tangles in the absence of excessive Aβ via the production of unstable tau isoforms that misfold, causing other types of neurodegenerative diseases (as in Hereditary Frontotemporal Dementia with Parkinsonism linked to chromosome 17- characterized by tangles but no plaques)
  - Given that in rarer forms of dementia the formation of tau filaments is a more general event leading to neuronal death, Aβ may be the specific initiator of the tau filaments in Alzheimer's Disease

Note: Most of the content on pages 15-19 does not appear to be addressed in the learning objectives.

9) Describe the current treatment strategy for dementia including education, behavioral interventions, and pharmacologic interventions

- Establish an alliance with patient and family
  - Education about diagnosis and how to manage problematic behaviors (wandering, suspiciousness, catastrophic reactions)
  - Support of caregivers
- Consider cholinergic therapy (donezepil, rivastigmine, Galantamine) and/or memantine therapy (NMDA receptor antagonist)
  - Only mild benefit
  - Expensive
  - Clinicians may still feel it is worth a trial
- Since vascular disease may be a risk factor for Alzheimer's and many patients have mixed dementia with both Alzheimer's pathology and cerebrovascular disease, **treat vascular risk factors** (hypertension, hyperglycemia, hypercholesterolemia, hyperlipidemia)
- Monitor for patient safety
  - Discuss issues related to falls, driving restrictions, safeguards against wandering, and intervene when necessary
- Follow cognitive status and treat comorbid medical and psychiatric problems
  - Delusions, agitation, delirium, depression, and sleep problems are the most common precipitant of nursing home placement; intervening may prevent or delay placement
  - Since relatively minor and easily treated medical problems (e.g. a urinary tract infection or constipation) might increase agitation or confusion even in the absence of acute delirium, one should look for and treat these conditions

- Look at medication list for drugs (e.g. anticholinergics for bladder spasm) that may contribute to confusion and negate benefit of cholinergics like Aricept
- Psychotropic medications might be used (see table 6-6 below)
- Antipsychotics (see below- LO #11)
- Since depression can present differently in patients with dementia (with more irritability and paranoia), consider an antidepressant trial (perhaps even before an antipsychotic)

Table 6–6. Pharmacologic Agents Useful in Treating Psychiatric Symptoms in Dementia

Symptom	*Medication*	*Special Considerations*
Depression	Tricyclic antidepressants	Anticholinergic side effects (impaired memory, confusion, constipation), orthostatic hypotension (increased fall risk), arrhythmia, and oversedation are risks. Titrate upward very slowly and monitor serum level and ECG. Desipramine and nortriptyline are the safest
	SSRIs	Increased anxiety, tremor, sleep disturbance are risks
	Mirtazapine	Appetite stimulant effects may be useful for cachectic patients; oversedation and orthostatic hypotension are risks
Anxiety	Benzodiazepines	Lorazepam and oxazepam don't have active metabolites. Confusion, over sedation, ataxia, memory disturbance, behavioral disinhibition are risks
	Buspirone	Dizziness, nervousness, headache, nausea are risks
Insomnia	Trazodone	Oversedation, priapism (low risk in older men) are risks
	Benzodiazepines	See above
Psychosis	Typical antipsychotics	Increased risk of tardive dyskinesia in elderly, parkinsonism (fall risk), akathisia (may contribute to increased anxiety/agitation), and oversedation are risks. Low doses (e.g., 0.5 mg/day) of higher-potency agents (e.g., haloperidol) preferred, despite greater risk of extrapyramidal symptoms, given their lower anticholinergic toxicity
	Atypical antipsychotics	Lower risk of tardive dyskinesia, less likely to require concomitant administration of anticholinergic medication. Sedation and extrapyramidal symptoms still risks
Aggression	Antipsychotics	See above. Also treat comorbid psychosis. Atypical agents may also treat aggressive, depressive, or manic symptoms. Because of greater neurologic risks, typical antipsychotic agents generally should be avoided if aggression is sole presenting symptom (i.e., in absence of psychosis). Periodic tapers should be attempted if patient stable
	Buspirone	See above. Delayed onset of effect (weeks). Less sedating than other options, but therefore may require use of second agent at night for sleep or "sundowning." Treats comorbid anxiety
	SSRIs	See above. Delayed onset of effect (weeks). Treats comorbid depression and anxiety
	Trazodone	See above. Treats comorbid sleep disturbance
	Anticonvulsants (carbamazepine/valproate)	Confusion, ataxia, bone marrow suppression, hepatoxicity are risks
	Lithium carbonate	Confusion and toxicity are risks, especially in patients with renal insufficiency or on drugs that raise levels (e.g. diuretics, ACE inhibitors). Monitor lithium levels, renal function, thyroid function
	Benzodiazepines	See above. Treats comorbid anxiety
	β-blockers (propranolol and others)	Best studied in patients with head injury. Slow onset of effects, and need for gradual upward titration. Exclude patients with asthma or COPD, diabetes, congestive heart failure, significant peripheral vascular disease, hyper thyroidism

time to get my glasses checked, huh? le swap; hopefully this one's clearer

10) Describe the recently proposed revision to the diagnostic criteria for Alzheimer's disease in order to allow for earlier diagnosis. (Controversial at this point, since there is no significantly effective therapy).

- Slowly progressive **memory impairment** documented on formal testing **plus one or more** of:
  - Medial temporal lobe atrophy on MRI
  - Abnormal CSF biomarker profile (low CSF levels of beta-amyloid, high levels of total tau protein, high levels of phosphorylated tau protein)
  - Reduced glucose metabolism in bilateral temporal parietal regions or increased Aβ radioligand uptake on PET
  - Proven autosomal dominant genetic mutation

11) Describe the risk of antipsychotic medication in treatment of agitation in dementia and the appropriateness of exploring other strategies for managing dementia including behavioral strategies and antidepressant medication

- Antipsychotics are among the most commonly prescribed agents in dementia, particularly for treating behavioral disturbances (despite being effective in only 20-30% of cases)
    - Associated with a small but statistically significant increased risk of cardiac arrhythmia and stroke
- FDA review of all atypicals except clozapine and ziprasidone showed 1.6-1.7 fold increase in mortality
    - Drug-treated patients: 4.5% rateFpick of death over 10 weeks
    - Placebo: 2.6% rate of death
- Recent longitudinal study (CATIE-AD) didn't find antipsychotic medication more effective than placebo over long-term use
- Conclusion
    - Anti-psychotics should be **reserved for severe agitation or psychosis**
    - Other alternatives should be considered
    - Antipsychotics should be tapered or discontinued over time if possible
    - All issues should be discussed with family
- Nursing homes have specific regulations prohibiting the use of antipsychotics for the convenience of staff (should be used only for specific target symptoms, other options should be considered first, and attempts should periodically be made to reassess need for them and whether the dosage could be tapered or the drug discontinued)

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Language
Kathleen Fuchs, PhD
Tuesday May 3, 2011 8:10 -9:00 am

There will be a ppt posted to the course website.

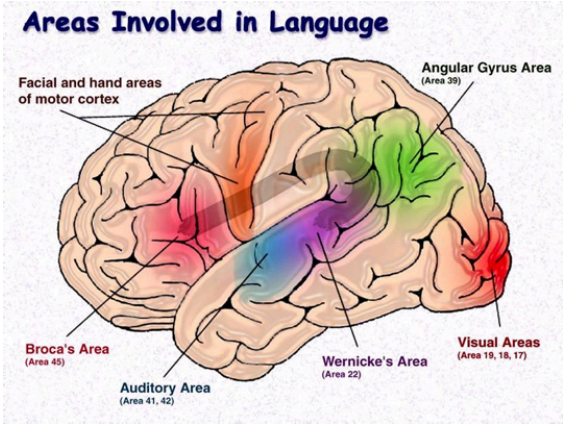
1. Distinguish between the left and right hemispheres in terms of dominance for the following aspects of language: speech generation, language comprehension, prosody, supra-ordinate language, automatic language.

- Left Hemisphere: Processing serial stringing of sounds to make words (phonology)
    - Speech Generation
    - Language Comprehension
- Right Hemisphere: "Higher Order" Control Aspects of Language (tone)
    - Prosody (rhythm, stress, intonation)
    - Supra-ordinate Language (e.g. jokes)
    - Automatic Language

2. Define aphasia, prosody, automatic language, motor aphasia, sensory aphasia, non-fluent aphasia, fluent aphasia

- Aphasia: Acquired disorder of symbolic language **processing**
    - Subtypes classified by relative impairments of different language domains
    - Separate from disorders of articulation (dysarthria), perception (deafness), thoughts (schizophrenia)
    - Most are actually "dysphasia"- language is not completely absent
    - Aspects that can be affected:
        - Syntax--grammatical structure of sentences
        - Lexicon--words available in a language that denote particular meanings
        - Morphology--how individual speech sounds (phonemes) are combined to form words
- Prosody: Rhythm, stress, and intonation of speech (Wikipedia)
- Automatic Language: reflexive in nature, like you stub your toe and say "crap" or "ow" without thinking about it;
- Motor Aphasia: Broca's Aphasia (see below)
- Sensory Aphasia: Wernicke's Aphasia (see below)
- Non-fluent Aphasia: Speech is broken up or slowed, but may retain contextually sensical words throughout (Broca's aphasia)
- Fluent Aphasia: Speech is fluent (normal pace) but meaningless; impaired ability to comprehend spoken or written words (Wernicke's aphasia)
    - *sounds* of speech come out fine, but the sounds are not formed into recognizable words (they're meaningless)
    - errors in semantics & word forms

3. Identify Broca's and Wenicke's areas of the brain. Predict the consequences of a lesion in Broca's area and in Wernicke's area. Name the fiber tract that connects Broca's and Wernicke's areas.



- Lesion to Broca's Area → Broca's Aphasia
- Lesion to Wernicke's Area → Wernicke's Aphasia
- Fiber Tract Connecting Broca's and Wernicke's Areas: **Arcuate fasciculus** (this appears to be the answer according to the PPT; however, Wikipedia says that new research suggests that this is not actually true: http://en.wikipedia.org/wiki/Arcuate_fasciculus)

I emailed Professor Fuchs the actual article on the arcuate fasciculus, her response:

"Interesting article and I wouldn't be surprised if eventually our conceptualization of the language "circuit" is altered. But for the purposes of the historical understanding (and an exam in this class) I'd go with:

The gross conceptualization is that it connects the **posterior language areas to the anterior ones**...as in :

....the arcuate fasciculus, an arching bundle of association fibers that courses through the frontal, parietal, and temporal lobes. The arcuate fasciculus, a part of the superior longitudinal fasciculus, **interconnects Wernicke's area (the posterior part of the superior temporal gyrus that is involved in the interpretation of spoken language) with Broca's area (the "motor speech" area in the posterior part of the inferior frontal gyrus, the opercular and triangular regions).** The arcuate fasciculus is thus essential for normal speech and language function. Note also the optic radiation: the bundle labeled here probably includes fibers of the inferior longitudinal fasciculus, an association fiber bundle that interconnects the superior, middle, and inferior temporal gyri with the occipital lobe; the optic radiation fibers are between it and the lateral ventricle."

4. Distinguish between the characteristics of Broca's aphasia and Wernicke's aphasia in terms of the following: characteristics of spontaneous speech, facility for naming, auditory comprehension and repetition.

- Broca's Aphasia (anterior Aphasia, non-fluent aphasia, Expressive Aphasia)
  - Spontaneous Speech
    - Non-fluent, hesitant, from mute to agrammatic, often dysarthric
  - Naming
    - Impaired (tip of the tongue)
  - Auditory Comprehension
    - Intact for simple material, impaired for complex syntactic constructions
  - Repetition
    - Impaired, hesitant
  - Reading
    - Difficulty reading aloud, often poorer reading than auditory comprehension
  - Writing
    - Difficulty writing, even with left hand (assumes Broca's area is on the left side)
  - Associated Signs
    - Right hemiparesis, right hemisensory loss
  - Behavior
    - Frustrated
    - Depressed

        - Appropriate
    - Features
        - Awareness of deficit
        - Frustration
        - Single words relevant to topic
        - Some automatic speech
    - Recovery
        - Significant right hemiparesis
        - Speech generation continues to be slow
        - Nouns and verbs intact but complex grammar impacts comprehension
- Wernicke's Aphasia (Sensory Aphasia, Posterior Aphasia, Fluent Aphasia, Receptive Aphasia)
    - Spontaneous Speech
        - Fluent with paraphasic errors of both phonemic and semantic type
    - Naming
        - Impaired, often paraphasic
    - Auditory Comprehension
        - Impaired, often for even simple questions
    - Repetition
        - Impaired
    - Reading
        - Usually impaired
    - Writing
        - Well-formed but paragraphic
    - Associated Signs
        - +/- Right hemianopia
        - Usually no motor or sensory abnormalities
    - Behavior
        - Often unaware of deficits, may be inappropriately happy, later sometimes angry, suspicious
    - Features
        - Unconcerned about/unaware of failure to communicate?
        - Able to follow some commands
        - Almost sounded like another language
        - May try to supplement with gestures
        - Perseverative?
        - Prosody and fluency intact

	Broca's Aphasia	Wernicke's Aphasia
Characteristics of Spontaneous Speech	Non-fluent, hesitant, from mute to agrammatic, often dysarthric	Fluent with paraphasic errors of both phonemic and semantic type
Facility for Naming	Impaired ("tip of tongue")	Impaired, often paraphasic (substituting words for others inappropriately)
Auditory Comprehension	Intact for simple material Impaired for complex syntactic constructions (ex "the cheetah was killed by the lion." when asked which animal died he/she will not know)	Impaired, often for even simple questions
Repetition	Impaired, hesitant	Impaired

Table that combines the above info:

	Broca's Aphasia	Wernicke's Aphasia
AKA	Motor Aphasia Anterior Aphasia Non-fluent aphasia Expressive Aphasia	Sensory Aphasia Posterior Aphasia Fluent Aphasia Receptive Aphasia
Characteristics of Spontaneous Speech	Non-fluent, hesitant, from mute to agrammatic, often dysarthric	Fluent with paraphasic errors of both phonemic and semantic type
Naming	Impaired (tip of tongue)	Impaired, often paraphasic
Auditory Comprehension	Intact for simple material Impaired for complex syntactic constructions	Impaired, often for even simple questions
Repetition	Impaired, hesitant	Impaired
Reading	*Difficulty reading aloud, often poorer reading than auditory comprehension*	*Usually impaired*
Writing	*Difficulty writing, even with left hand (assumes Broca's area is on the left side)*	*Well-formed but paragraphic (i.e. can write letters but will string them together to produce meaningless words)*
Associated Signs	*Right hemiparesis, right hemisensory loss*	*+/- Right hemianopia* *Usually no motor or sensory abnormalities*
Behavior	*Frustrated* *Depressed* *Appropriate*	*Often unaware of deficits, may be inappropriately happy, later sometimes angry, suspicious*
Features	*Awareness of deficit* *Frustration* *Single words relevant to topic* *Some automatic speech*	*Unconcerned about/unaware of failure to communicate?* *Able to follow some commands* *Almost sounded like another language* *May try to supplement with gestures* *Perseverative?* *Prosody and fluency intact*
Recovery	*Significant right hemiparesis* *Speech generation continues to be slow* *Nouns and verbs intact but complex grammar impacts comprehension*	

5. Distinguish between the perisylvian areas anterior to and posterior to the central sulcus in terms of their roles in perception of speech, production of speech, expression of speech and comprehension of speech.

- Posterior to central sulcus: Perception and comprehension
- Anterior to central sulcus: Production and expression

Wernicke-Geschwind Model of brain regions involved in language:
1) Wernicke's area takes sensory information and performs computations to extract out linguistic significance.
2) The arcuate fasciculus is a direct path from Wernicke's area to Broca's area.
3) Broca's area takes ideas and performs computations to turn them into instructions for movement that will have linguistic significance (i.e. that someone else's Wernicke's area can decode!)

6. Distinguish between global aphasia and Wernicke's and Broca's aphasia.

- Global Aphasia

- Spontaneous Speech
  - Non-fluent, mute, or restricted to a stereotyped phrase
- Impaired
  - Naming, auditory comprehension, repetition, reading, writing
- Associated Signs
  - Must have <u>right hemianopia</u>
  - <u>Right hemiparesis</u>
  - <u>Right hemisensory loss</u>
  - Often apraxia
- Behavior
  - Often depressed
- Prognosis
  - Often improves over time
  - Most common evolution
    - Global → Broca's aphasia
    - Sometimes → Wernicke's or anomic aphasia

Summary of the Main Aphasias (with Perisylvian Areas Affected)

Syndrome	Spontaneous Speech	Comprehension	Repetition	Naming
Broca's	Non-fluent ("Telegraphic")	Good	Poor	Poor
Wernicke's	Fluent (semantic & phonemic paraphasias)	Poor	Poor	Poor
Conduction	Fluent (semantic paraphasias)	Good	Poor	Poor
Global	Non-fluent	Poor	Poor	Poor

7. Name the artery(s) that supplies language areas of the brain.

Middle Cerebral Artery

a. *Most frequently vascular (ischemic)*
   i. ***<u>For perisylvian aphasias: MCA or its branches</u>***
      1. *For Broca's aphasia: usually embolic cause; younger patients*
      2. *For Wernicke's aphaisa: usually thrombotic; older patients*
   ii. *For other aphasias: Borderzone ("watershed") infarcts*
      1. *Post cardiac arrest, hemodynamic*
      2. *CO intoxication, anoxia, prolonged hypoglycemia*
b. *Subcortical:*
   i. *Hypertensive bleeds or ischemia of branch arteries*
c. *Others:*
   i. *Tumors, trauma, infection, degenerative disease*

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Aging and Loss
Nassima Ait-Daoud Tiouririne MD
Tuesday May 3, 2011 9:30-10:40 am

Required reading: Handout posted to course website.

1. List important factors that affect life expectancy. FHx of longevity, physical activity, employment, advanced education, social support

2. Describe the psychological changes that occur with aging. Erickson's ego integrity vs despair: satisfaction & pride in one's past accomplishments vs. a sense of worthlessness & despair.

3. List brain changes that accompany aging. Atrophy (gray matter thinning + white matter degeneration), increased ventricular and sulci spaces, decreased cerebral blood flow, decreased brain weight, gyral atrophy, changes in morphology of neurons (e.g. decreased size & # of dendritic spines and arbors of cortical pyramidal neurons), senile plaques & neurofibrillary tangles.

4. Describe important cognitive changes which occur with aging.
Acquiring new memories of events or facts, short term memory, working memory and processing speed are relatively impaired and tend to decline in old age.
Autobiographical (episodic) memory, emotional processing, and procedural memory remain stable. Semantic memory, such as vocabulary may even improve w/ age.

5. Describe brain physiological changes that occur with aging

- **Calcium regulation** changes-->change in neuronal firing and the ability to propagate action potentials--> less brain plasticity.
- **Dopamine**: decline in dopamine synthesis mostly in the striatum & fewer D1, D2 and D3 receptors-->neurological sxs that increase with age (decreased arm swing, increased rigidity, change in cognitive flexibility).
- **Serotonin**: Decreasing levels of different serotonin receptors and the serotonin transporter, 5-HTT
- **Glutamate**: lower glutamate concentration in the motor cortex, esp parietal gray matter, basal ganglia & frontal white matter.
    - Less availability of NE, GABA, & ACh
    - Increased availability of MAO

6. Describe the various pharmacokinetic and pharmacodynamic changes that occur with aging and how they affect certain medications (benzodiazepine, narcotics, beta blockers, digoxin and anticholinergics).

Absorption: *rate* of absorption delayed with lower peak concentration and delayed time to peak concentration; overall amount absorbed (bioavailability) unchanged

Bioavailability: first-pass metabolism drugs are more **bioavailable** b/c less drug is extracted by liver (less liver mass & liver blood flow)

Distribution: elderly patients have:

- A lower percentage of body water. Drugs such as alcohol that distribute in water will have higher levels because the volume of distribution is smaller.
- A lower lean body mass: drugs that bind to muscle such as digoxin will have a lower volume of distribution
- More body fat. Lipid soluble drugs such as diazepam and trazodone will have longer half-lives b/c storage reservoir is greater.
- Reduction in plasma albumin: this will cause an increase in percentage of unbound or free drug (active) for those that bind albumin such as diazepam, valproic acid and warfarin.
- Renal excretion as measured by Glomerular Filtration Rate (GFR) decreases by about 50% by age 70 so this will affect all the

drugs that are excreted by the kidneys.

Pharmacodynamic (the time course and intensity of pharmacological effect of a drug).

- Increased sensitivity to sedation with benzodiazepines
- Increased level and duration of pain relief with narcotics
- Increased sensitivity of anticholinergic agents
- Increased cardiac sensitivity to digoxin.
- Decreased heart rate response to beta blockers

Pharmacokinetic & pharmacodynamic changes result in **decreased clearance & increased sensitivity** to meds in elderly so start at low doses and raise doses more slowly.

7. Differentiate between depression and dementia in the elderly.

- **Depression**: Most common psychiatric disorder in the elderly with suicide becoming more common than in the general population
    - **Pseudodementia**: Depression mimicking dementia because of its associated cognitive decline; treatable with antidepressants (unlike dementia)
- **Dementia**: Gradual and inexorable development of cognitive decline manifested by impairments in memory, abstract thinking, judgment, personality, and the performance of complex motor tasks
- Common problems that mimic dementia
    - Grief
    - Major depressive episode
    - Medication-induced toxic encephalopathy

	Depression	Dementia
Mental Decline	Rapid	Slow
Orientation	Preserved	Lost
Language and motor skills	Slow but normal	Impaired
Memory problems	Notices and worries about memory problems.	Does not seem to notice memory problems
Sadness	Pervasive, may be suicidal	Intermittent
Insomnia	may be severe early morning awakening	may be severe throughout the night
Anorexia	may be profound	"forgets to eat"
Self-image	feelings of worthlessness	confused
Guilt	morbid preoccupations with present and past transgressions	confused
Psychosis	mood-congruent delusions and hallucinations	disorganized

8. Differentiate between normal and unresolved grief.

- Normal Grief: Psychobiological response to the loss of someone close that lasts 1-2 years (may return around holidays, anniversaries)
    - Characterized by shock & denial initially
    - Normal to experience an *illusion* that deceased person is physically present
- Unresolved Grief: Symptoms persist beyond the cultural norm (1-2 years)
    - Does not lessen or pass with time
    - Patient appears to make no progression toward the resolution of grief
        - Patient may keep the deceased person's room unchanged or set a place for him/her at the dinner table
    - Can be termed abnormal/complicated grief reaction or depression

Grief Reaction	Normal(Bereavement)	Abnormal (depression)
Weight loss	Minor	Significant (>5% of body weight)
Sleep disturbances	Minor	Significant
Guilt	Mild	Intense
Perceptual disturbances	Illusions	Hallucinations
Social integration	Resumes	Isolate self
Anhedonia	Not prolonged	Present and prolonged
Sadness	Varies from time to time	Constant
Low self esteem	Not typically present	Present
Suicidal ideation	Not present or passive	Considers seriously or attempts
Duration of severe sxs	Within 2 months	Greater than 2 months
Duration of moderate sxs	Within one year	Greater than one year
Treatment	Mainly supportive and symptomatic	Requires antidepressants and sometimes antipsychotics and ECT

9. List and describe the Kubler-Ross stages of dying.

- **Denial**: Refusal to believe the news
- **Anger**: Patient may become angry at the physician
- **Bargaining**: Trying to strike a bargain with the doctor, God, etc.
- **Depression**: Patient becomes preoccupied with death and becomes emotionally detached; overwhelming feeling of hopelessness
- **Acceptance**: Patient accepts his/her fate

It is important to know that patients do not go through these stages in a linear sequential manner. They may demonstrate behaviors related to all five stages during a single interview, or they may go through a rather "stageless" process dominated by a single one of the five stages or they may fluctuate back and forth.

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Review
Mary Kate Worden PhD and Bart Nathan MD
Tuesday May 3, 2011
10:40-11:10 am

Drs Worden and Nathan will take questions from students. There is no formal structure for this review session. We will be happy to answer questions on any learning objectives from Mind Brain and Behavior.

Did anyone who stayed learn anything interesting or helpful? Nope.

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Childhood Disorders
Bruce Cohen, MD
Monday May 2, 2011 10:10-11AM

Before class:
Required:
1) Theory and Practice of Psychiatry. Chapter 19: Childhood Disorders pp 482-509
2) Childhood Disorder Supplemental Handout (on the website). Provides some updated information on medication for ADHD.
3) Mood Disorder Handout (on class website, previously distributed with mood disorder lecture), pp. 32-35.

1) Contrast how the assessment of children for psychiatric disorders differs from assessment of adults (note: in addition to pages 482-483, use page 508, under "The Life Story Perspective").

- Examining children is more difficult because they are unable to fully examine their feelings and are more prone to demonstrate psychiatric disturbances through problematic behavior.
- In assessing children, work backwards, assemble data from multiple sources, supplement history with descriptions of behavior from parents and teachers
- Use ancillary studies (e.g. intelligence testing, projective testing) because sometimes children only express how they feel indirectly (Ex: drawings and free play)
- Children are NOT "little adults"
- Children with one disorder are found to have several co-morbid disorders (ADHD occurs with Learning Disabilities)
- Childhood disorders may not be pathological for children who are at one stage of development, but if they persist or return beyond that stage are considered abnormal
- Children have not developed a life-story as in adults, and externalize via conduct and behavior difficulties, despite not appreciating their own attitudes or current life difficulties.
- In childhood, psychotherapy may have a preventative instead of a reparative function.
- Many children present for treatment only because they are forced to by their parents, which may interfere with their receptiveness of therapy
- Treatment tends to be more directive and less interpretive with children
- Parents may reinforce the child's behavior unintentionally, and may become angry at the clinician for "blaming them"

2) Contrast how the following psychiatric disorders present in childhood vs. adulthood:
a) Mood disorder (depression, bipolar disorder)

- Major Depressive Disorder
    - May present with conduct problems or irritability
    - Preadolescent children with major depressive disorder are less likely to demonstrate hypersomnia, weight loss, or delusions. They are more likely to present with prominent **somatic complaints**, **irritability**, and **social withdrawal**
    - Treatment
        - First Choice: Individual/Family psychotherapy
        - SSRIs are safest first choice medication
        - TCAs associated with cardiac toxicity, case reports of sudden death with desipramine
- Bipolar Disorder
    - Typically has an earlier age of onset than MDD
    - Depression may precede any manic episodes
    - Can be difficult to distinguish manic episodes from ADHD or depression because **80% of episodes are "atypical"** (vs. 20% in adults)
        - While "atypical" forms of mania (mixed or dysphoric mania, or rapid cycling between mania and depression) are the exception in adults (about 20% of cases), they are the rule in children (about 80% of cases)
    - Irritable with temper outbursts in the manic state, rather than euphoric mood

    - Chronic and continuous rather than intermittent and acute
    - 20% of children with ADHD ultimately developed Bipolar Disorder in one longitudinal study
    - Treatment: Lithium best studied for Bipolar in children but clinicians use anticonvulsants (carbamazepine and valproate) as well
- Assess for comorbid conditions (80-95% of depressed youths have comorbid condition), similar to adults
    - Dysthymic (same criteria as for adults but only 1 year duration)
    - Separation Anxiety (vs. GAD in adults)
    - Conduct Disorder (vs. Substance Abuse in adults)

b) OCD

- 1/3-1/2 of cases begin in childhood
- May not report obsessive thoughts, only rituals
- Treated with behavior therapy; clomipramine or SSRIs

c) Panic Disorder

- Less likely to report "classic" fears of dying, going crazy, or doing something uncontrolled
- Treatment typically involves psychotherapy augmented with benzodiazepines, TCAs, or SSRIs

d) PTSD

- Presents with separation anxiety, fears of death, and social withdrawal
- Reexperiencing through nightmares, daydreams, or repetitive reenactments of the trauma in symbolic play, rather than intrusive flashbacks
- May regress to behavior from an earlier developmental stage
- May experience somatic symptoms, especially headaches and stomach aches
- Treatment typically involves individual and family therapy, possibly including attempts at systematic desensitization
- Pharmacological interventions less studied in children; anecdotal reports of propanolol

e) Generalized Anxiety Disorder

- 3% of school-aged children
- Half of all patients with GAD report onset during childhood
- Previously called "Overanxious Disorder of Childhood"
- Appear shy and self-deprecating
- Multiple somatic symptoms
- May engage in stereotyped nervous habits, e.g. nail biting, hair pulling, or thumb sucking
- Treatment typically involves behavioral therapy in younger children and cognitive therapy in older children, emphasizing assertiveness training
- Parents also are often anxious and family therapy can be useful
- Antihistamines have often been prescribed although there are no data suggesting that these are efficacious (likely used because they are sedating)
- SSRIs, benzodiazepines, and buspirone have also been utilized in clinical practice

f) Social Phobia

- Social phobia in 1% of children
    - Previously "Avoidant Disorder of Childhood"
- Few controlled pharmacologic studies in children → clinicians typically try agents that have been successful in adults (SSRIs, benzodiazepines) in combination with psychotherapy

g) Schizophrenia

- Rare (0.014% of children), but described in children as young as age 5 (almost all cases demonstrate onset after puberty)
- Diagnostic criteria are the same as for adults
- Early onset may select for a more homogeneous group, with either a stronger genetic or perinatal-insult component or with hormonal abnormalities that predispose an individual who would have developed symptoms of the illness at a later date to do so earlier than would have been expected
- Primarily male children
- Typically both positive and negative symptoms, including flat or inappropriate affect, deterioration of function, prominent hallucinations and delusions, avolition, and alogia
- Onset typically insidious, with prodromal deterioration in school performance, social withdrawal, disorganized behavior, and decreased ability to perform activities of daily living such as personal hygiene

- Response to medications and overall outcome tends to be poor

3) Separation anxiety disorder:

a) Distinguish between developmentally normal separation anxiety and the diagnosis of separation anxiety disorder.

- Normal separation anxiety first appears by about age 7 months and peaks at 13-18 months before gradually subsiding
- Anxiety in Separation Anxiety Disorder is greater than would be expected normally; patients experience severe anxiety upon separation from home or major attachment figures

b) Distinguish between behavioral inhibition as a feature of temperament/personality and separation anxiety disorder as how this predisposition manifests itself behaviorally. Also distinguish between how somatic complaints might present with generalized anxiety disorder vs. separation anxiety disorder.

- Patients often are shy and inhibited
- Becomes more apparent at about age 7 or 8, with refusal to go to school, to friend's house for sleepovers, or to camp
- Patients may "shadow" or "cling to" their parents
- In contrast to GAD, somatic complaints are linked to either separation or anticipation of impending separation
- Diagnostic Criteria: 3+ of the following
    - Recurrent excessive distress when separation from home or major attachment figures occurs or is anticipated
    - Persistent and excessive worry about losing, or about possible harm befalling, major attachment figures
    - Persistent and excessive worry that an untoward event will lead to separation from a major attachment figure (e.g. getting lost or being kidnapped)
    - Persistent reluctance or refusal to go to school or elsewhere because of fear of separation
    - Persistently and excessively fearful or reluctant to be alone without major attachment figures at home or without significant adults in other settings
    - Persistent reluctance or refusal to go to sleep without being near a major attachment figure or to sleep away from home
    - Repeated nightmares involving the theme of separation
    - Repeated complaints of physical symptoms (such as headaches, stomachaches, nausea, or vomiting) when separation from major attachment figures occurs or is anticipated

c) List other comorbid conditions that commonly occur along with separation anxiety disorder

- Social Phobia
- Generalized Anxiety Disorder
- Panic Disorder
- Major Depressive Disorder
- Dysthymic Disorder
- Cluster C Personality Disorders

d) Describe what genetic and/or environmental family factors might contribute to the development of separation anxiety disorder in a child.

- Often come from families with significant histories of anxiety, including higher familial rates of panic disorder
- Mothers of these children have "insecure attachments" themselves, anxious with separation from the child, overly preoccupied with child's somatic symptoms, ambivalent about sending the child off to school

e) Describe how even with "successful" short-term treatment for such a problem, anxiety usually still persists and presents later in life in various other contexts. In what other situations might you expect the patient to have problems and what other disorders might they be diagnosed as having?

- Chronic course
- Even when coaxed to school, they still tend to be underachievers
- Similar picture as adults at work: absenteeism, poor performance
- Difficulty handling major life changes (e.g. moving or getting married), and may be overly concerned about the safety of spouses and their own children
- Many will ultimately develop other anxiety disorders
- Retrospective studies of adult Panic Disorder patients revealed those with histories of Separation Anxiety Disorder as children had earlier onset of Panic Disorder and more severe symptoms

f) Distinguish "school refusal/absenteeism" as a behavior (i.e. refusing to go to school) from separation anxiety disorder and list some other disorders that also can contribute to a child refusing to go to school.

- Separation Anxiety Disorder only one possible cause of this
- 75% of adults report having failed to go to school at some point, and in some inner city schools, absenteeism is as high as 90%
- Some cases due to **Conduct Disorder**, others due to Separation Anxiety Disorder, Generalized Anxiety Disorder, Panic Disorder with Agoraphobia, Social Phobia, MDD, Dysthymia
- Could reflect an underlying Learning or Communication Disorder

g) Describe how you would treat a child presenting with separation anxiety disorder with school refusal and difficulty going to sleepover parties. Include behavioral strategies and potential pharmacologic options.

- For "school refusal," behavioral interventions
    - Progressive exposure to school
    - Coin to page parents can be useful (I think this means 'give the child change in order to use a pay phone to call mom or dad' if they begin to feel anxious. It would allow the child to feel like there was a fail-safe) A coin to page the parents? Are we assuming people still use payphones and the kid's parents are doctors? lol what a funny phrase I can imagine what this could mean otherwise. Update for 2011: cell phone to call parents (you can tell Cohen wrote this like 15 years ago cause ppl had to use payphones and normal people could only afford beepers/pagers).
- More than just a behavior disturbance given pervasive anxiety
    - Individual psychotherapy: help develop autonomy and self-esteem
    - Educate parents about the need to be supportive without being overly indulgent and reinforcing child's fears
    - Sometimes a parent needs to be treated for an anxiety disorder
- Pharmacotherapy in more severe cases
    - SSRIs have supplanted TCAs; Buspar also tried
    - Benzodiazepines, beta-blockers for anxiety with exposure
- With treatment, most children no longer meet criteria for separation anxiety disorder within the next year but many of these children continue to be fearful, avoidant, and at risk for the development of another anxiety or mood disorder

4) Define selective mutism, distinguish it from the developmentally normal mutism around strangers seen in children from around ages 3-5, and list contributing factors and treatment options for selective mutism.

- From about age 3-5, most children are briefly mute around strangers
- **Selective Mutism:** This behavior persists and increases in severity (after age 5? that is, is presentation after age 5 then a sign of selective mutism?)
    - Failure to speak in specific social situations despite being able to speak in other situations (distinguishing it from Language Disorder, Autism, or Mental Retardation)
- Rare (0.03-0.08% of children), most commonly diagnosed between 5-8 years
- Almost all show behavioral inhibition and also have Social Phobia beyond mutism itself
- About a third have a Language Disorder and half had delayed speech development; may shape presentation
- Family dynamics similar to those in Separation Anxiety Disorder
- Treatment: Individual/family/behavioral therapy, augmented with medication (usually SSRI)

5) Describe the symptoms of reactive attachment disorder (both the inhibited type and the disinhibited type), the types of pathogenic care that can lead to reactive attachment disorder (note that "pathogenic care" is not synonymous with child abuse, since a child who has had frequent changes in foster care settings or has been in and out of the hospital also can develop such symptoms) and how you might attempt to address the disorder (in terms of both medical intervention and social intervention) in the office or ER setting.

- Pathogenic Care, either
    - Persistent disregard of the child's basic emotional needs for comfort, stimulation, and affection; or
    - Persistent disregard of the child's basic physical needs; or
    - Repeated changes of primary caregiver that prevent formation of stable attachments (e.g. frequent changes in foster care)
- Leading to either (symptoms):
    - **Reactive Attachment Disorder - Inhibited Type**: Persistent failure to initiate or respond in a developmentally appropriate fashion to most social interactions (excessively inhibited, hypervigilant, or highly ambivalent and contradictory responses)

    - **Reactive Attachment Disorder - Disinhibited Type**: Diffuse attachments as manifest by *indiscriminate sociability* with marked inability to exhibit appropriate selective attachments (e.g. excessive familiarity with relative strangers or lack of selectivity in choice of attachment figures)
- Treatment
    - Treat medical complications: malnutrition, dehydration, infection
    - May require removal of child from the home
    - When less emergent: family education, psychotherapy, increased social supports

6) Pervasive Developmental Disorders:

a) List the three areas of impairment seen in pervasive developmental disorders (with autistic disorder, in which all 3 types of impairment are present, being the prototypical disorder) as well as potential associated features.

- Deficits in reciprocal social interaction
    - Impaired nonverbal communication (eye contact, facial expression, body postures, and gestures)
    - Failure to develop peer relationships
    - Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people
    - Lack of social or emotional reciprocity
- Deficits in communication
    - Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
    - In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
    - Stereotyped and repetitive use of language or idiosyncratic language
    - Lack of varied, spontaneous, make-believe play or social imitative play appropriate to developmental level
- Presence of stereotyped behavior, interests, and activities
    - Preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
    - Apparently inflexible adherence to specific, nonfunctional routines or rituals
    - Stereotyped and repetitive motor mannerisms (hand or finger flapping/twisting, complex whole-body movements)
    - Persistent preoccupation with parts of objects
- Associated Features
    - Mental retardation common, but distribution of deficits often very uneven, with islands of intact or even very high functioning (although "savants" are rare)
    - May have seizures
    - Hyperactivity, short attention span, impulsivity, aggressiveness, self-injurious behaviors (e.g. head banging or biting of the hands) and (particularly in young children) temper tantrums
    - Unlike Childhood Schizophrenia: younger onset, no loose associations, no hallucinations/delusions

b) Distinguish between autism and childhood schizophrenia.

(Unlike childhood schizophrenia, there is a younger onset, and different pattern of deficits, as well as no psychosis [i.e., no loose associations, no hallucinations, and no delusions].)

c) Describe how you would work up a child (physical exam, psychological testing, ancillary tests) presenting with these symptoms.

- Likely genetic component, but also sometimes prenatal insult (rubella, phenylketonuria, tuberous sclerosis)
- Physical Exam
    - Measurement of head circumference
    - Minor physical anomalies (more common in autism)
    - Skin changes typical of tuberous sclerosis ("ash leaf patches," adenoma sebaceum, "shagreen patches")
    - Neurologic exam
    - Visual acuity or hearing testing
- Neuropsychological testing to delineate the extent of cognitive and communication impairment
- MRI and EEG to rule out other illnesses (typically nonspecific in Autism)
- Blood tests for lead, inborn errors of metabolism, and chromosomal studies (fragile X screen)
- Theorized link to childhood vaccination
    - Reviews of the evidence by several panels of experts have concluded that current evidence does not support this

theory - from assigned reading

d) Describe the treatment of autistic disorder including the following:

(1) Special educational and support services- <u>ESSENTIAL</u>
(2) Treat comorbid Mood Disorders, Anxiety Disorders (especially Panic and Obsessive-Compulsive Disorders), and Attention-Deficit Hyperactivity Disorder
(3) Behavior therapy to control self-injurious or other problematic behaviors
General Notes:

- Variable course, often with gradual improvement if supportive setting, but not uniform improvement across spectrum of symptoms and may occur in fits and starts
- Improvement influenced by IQ and severity of Autistic symptoms

e) Distinguish between Asperger's Disorder, Autism, Schizoid Personality Disorder, and "normal" social awkwardness

- **Asperger's Disorder**
  - do not demonstrate significant language dysfunction (although somewhat abnormal due to the intrusion of idiosyncratic preoccupations with certain topics, excessive verbosity, and inability to follow normal conversational conventions) or significant delays in cognitive development
  - are able to acquire age appropriate learning skills and adaptive behaviors *except* for the realm of interpersonal functioning
  - **eccentric and one-sided social approach** (e.g., pursuing a particular conversation topic regardless of other's interest)
    - autism shows complete social and emotional indifference
  - usually do not have mental retardation as in autism
  - usually present upon not "fitting in" with same age children
- **Schizoid personality disorder**
  - Asperger's is more severe and an earlier onset
- **"normal" social awkwardness**
  - Asperger's should only be diagnosed if a child's social deficits are severe and if the preoccupations are all-encompassing and interfere with the acquisition of basic skill

7) Attention-deficit hyperactivity disorder (ADHD):
a) List symptoms of ADHD within the two main clusters of symptoms (inattention and hyperactivity-impulsivity) that occur in ADHD. Describe how ADHD presentation can differ in girls vs. boys and why girls may be under-diagnosed while boys might be over-diagnosed.

- **Inattention Symptoms**
  - Poor attention to details; careless mistakes in schoolwork, work, or other activities
  - Difficulty sustaining attention in tasks or play activities
  - Doesn't seem to listen when spoken to directly
  - Doesn't seem to follow through on instructions; fails to finish schoolwork, chores, or workplace duties (not due to oppositional behavior but due to failure to understand instructions)
  - Difficulty organizing tasks and activities
  - Avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort (schoolwork)
  - Loses things necessary for tasks or activities (toys, school assignments, pencils, tools, books)
  - Easily distracted by extraneous stimuli
  - Often forgetful in daily activities
- **Hyperactive-Impulsive Symptoms**
  - Hyperactivity
    - Fidgets with hands or feet or squirms in seat
    - Leaves seat in classroom or in other situations in which remaining seated is expected
    - Runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
    - Difficulty playing or engaging in leisure activities quietly
    - "On the go" or often acts as if "driven by a motor"

        - Talks excessively
    - Impulsivity
        - Blurts out answers before questions have been completed
        - Difficulty awaiting turn
        - Interrupts or intrudes on others (butts into conversations or gestures)
- While ADHD once was believed to be more common in boys (with the sex ratio of boys to girls variously estimated at anywhere from 3:1 to 9:1), it now appears that ADHD simply is underdiagnosed in young girls, who are less likely to demonstrate hyperactivity, oppositionality, or delinquent behavior than boys and are more likely to present with inattention, impaired school performance, and underachievement. In adolescent and adult populations, ADHD is diagnosed as frequently in females as in males.

b) Describe the steps that one should take to try to insure that one is making an ADHD diagnosis with reliability (i.e., not overdiagnosing it, but also not minimizing the significance of symptoms and therefore underdiagnosing it)

- Must be frequent behaviors, present in multiple contexts (home, school, work), leading to impairment
    - Distinguish from "normal" developmental hyperactivity or effects of large classroom sizes
- Must be present **before age 7**
    - Developmental history therefore necessary for adults
    - Distinguish from Hypomania, Depression, Personality Disorders
- Two clusters of symptoms, should have 6 or more symptoms of one of these (or both)
    - Inattention
    - Hyperactivity-Impulsivity

c) Describe the evidence that suggests that ADHD is a valid diagnosis and not simply a cultural fad. Include both genetic evidence and neurobiologic evidence that indicates that ADHD likely is a developmental disorder (albeit one that varies in the degree of severity of its symptoms and that can overlap at the margins with ordinary inattentiveness and with other psychiatric conditions).

- Likely chronic biologic vulnerability, with genetic component
- Places individuals at greater risk of
    - School failure/underachievement, Conduct Disorder, Substance Abuse, Depression
- **3-5% of children**; persists into adulthood in up to half
    - Hyperactivity declines but inattention persists
- No evidence that diet plays a role (sugar, Aspartame, trace elements, preservatives)
- Likely genetic component based on family studies, twin studies, adoption studies
- Dopamine System Hypofunction?
    - DA involved in attention and novelty seeking
    - Stimulants lead to improvement
    - Restlessness resembles akathisia
    - In families with history of ADHD, genetic defects noted in dopamine transporter gene (chromosome 5) and D4 receptor gene D4DR (chromosome 11)
- NE and 5HT may also play a role
    - NE involved in arousal and responsiveness to reinforcement
    - 5HT involved in inhibition of drives and impulses
- Final pathway may be *regional* imbalances, especially decreased frontal lobe activity

d) Describe the potential overlap of ADHD symptoms with those of depression, bipolar disorder, and learning disorder. Give an example of why it is important to routinely monitor symptoms over time, since the clinical presentation can change and necessitate a significant change in the diagnosis and in the treatment plan.

- Behavioral disinhibition, inattention, irritability, and hyperactivity are relatively nonspecific psychiatric symptoms that also occur, for example, in childhood major depressive disorder, childhood bipolar disorder, and learning disorders
- 20%–30% of depressed youth and 50%–90% of bipolar youth also fulfill the diagnostic criteria for ADHD
- Given that all of these other conditions are increasingly being recognized as being lifelong neurodevelopmental disorders, it may be quite reasonable to diagnose both ADHD and the other, comorbid, condition
- Often, these other psychiatric disorders ultimately will "declare themselves" at some later point when more specific symptoms finally appear (depressive symptoms, manic symptoms, panic attacks, etc.). Given this, clinicians must continually reassess children who they are treating for presumed ADHD at regular intervals

e) List the risks and benefits of treatment of ADHD with stimulant medication, with the norepinephrine reuptake inhibitor

atomoxetine (Strattera), with antidepressant medications, and with alpha-2 agonist medications (clonidine, guanfacine). [See also the Childhood Disorder Supplemental Handout on the website, which has information on atomoxetine that isn't in the textbook]

- **Stimulants:** dextroamp hetamine, methylphenidate, and mixed amphetamine salts
    - Schedule II controlled substances b/c of potential for abuse (but appears that the risk of addiction is overstated)
    - Rapid onset of action but short duration of effect (shorter than lifespan of drugs) ==> requires dosing several times per day (problems due to short duration of effect minimized w/ longer acting, delayed release preparations)
    - 70% of adult & child patients respond to methylphenidate (concerta, ritalin) or dextroamphetamine (dexedrine, dextrostat)
    - Side effects:
        - decreased appetite (with the potential for a delay in gaining weight in children), insomnia, and tachycardia
        - higher doses can lead to sedation or psychotic symptoms (esp hallucinations)
        - develop motor tics or exacerbate preexisting tics (e.g. w/ Tourette's Disorder)
- **Clonidine,** an a-2 agonist, is helpful especially **when ADHD accompanies a tic disorder** and stimulant therapy has been associated with exacerbation of the tics. Unfortunately, it is highly sedating for some patients.
    - **Guanfacine** (Tenex), a related medication, is longer acting and less sedating.
- While SSRIs sometimes are useful in treating impulsiveness and aggressiveness in children and adults, they appear to have little or no effect on core attention deficits associated with ADHD
    - sometimes are prescribed in combination with a stimulant when ADHD is associated with comorbid major depressive or dysthymic disorder and/or anxiety disorder
- **Atomoxetine** (selective norepinephrine reuptake inhibitor) has a magnitude of clinical improvement that appears to be a bit less than with stimulants. Improvement is more noticeable to patients who previously have been treated with stimulants than to "fresh cases" starting on atomoxetine as their first treatment
    - not a controlled drug, so can be refilled over the phone and can give samples

f) Imagine that you are working in a college student health clinic and a student with no past history of a diagnosis of ADHD comes to you saying that he thinks that he has ADHD that's never been treated. He says that he got by "without having to study" in high school, but that college is a lot harder, and he now is asking you to prescribe stimulant medication for him since he fears failing his classes otherwise. He has no history of substance abuse. Using information from pages 297 and 501-502 of the textbook, design an appropriate way of diagnosing the condition and of monitoring the treatment if you do elect to prescribe a stimulant.

- There is a fair amount of stimulant use by adolescents
- Abuse of methylphenidate by patients with ADHD or their family members is rarely reported
- Since epidemiological studies using standardized diagnostic criteria suggest that 3-6% (or even higher) of the school-aged population may have ADHD, the percentage of American youth being prescribed stimulants is at the lower end of the prevalence range
- While clinicians should be circumspect about prescribing stimulants, they shouldn't shy away from using them to treat patients who have ADHD
- Before initiating treatment, take a careful history, attempt to distinguish symptoms of ADHD from normal developmental behavior, and from symptoms of other psychiatric conditions
- Design an individualized treatment plan that takes into account the patient's symptoms, the extent of social morbidity, any comorbid psychiatric conditions, and the preferences of the patient/patient's family
- Treatment plan might involve a combination of medication, education, behavioral management strategies, and environmental interventions
- There should be appropriate follow-up, including monitoring for efficacy of medications, for adverse effects, and for ongoing need for treatment
- Document diagnostic assessment and treatment plan
- Given risk of abuse or diversion, physician should keep record of medication prescribed and should consider alternatives to stimulants in patients at high risk due to comorbid substance abuse or conduct disorder or because of family members with substance abuse

8) Conduct Disorder:

a) Define conduct disorder

- a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or values are violated

b) List the behaviors that can be seen in conduct disorder

- 3 (or more) must be present during the past 12 months and at least 1 in the past 6 months.
    - aggressive conduct that causes or threatens physical harm to other people or animals
    - non-aggressive conduct that causes property loss or damage
    - deceitfulness or theft
    - serious violations of rules

c) Describe the percentage of cases that go on to meet the adult diagnosis of antisocial personality disorder.

- 50%

d) List factors that can contribute to the development of a conduct disorder and factors associated with a poorer prognosis.

- genetic and biological factors appear to play a predisposing role in the development of the disorder
- learning disorder, communication disorder, ADHD: commonly predate the onset of conduct problems
- parental rejection and neglect, inconsistent child-rearing practices, harsh discipline, physical or sexual abuse, lack of supervision, early institutional living, frequent changes in caregiver, large family size, association with a delinquent peer group, and familial psychopathology

e) Describe the goals of treatment and how treatment may require "wrap-around" services including parents, doctors, therapists, the school system, the department of social services, and the legal system.

- Goal of treatment is to help parents and school officials set limits on the child's behavior (behavioral management), to treat comorbid psychiatric problems (especially ADHD, learning and communication disorders, mood disorders, and substance related disorders), and to use psychotherapy to attempt to teach the patient more appropriate and effective coping skills.
- Behavioral management is often hindered by parental psychopathology or domestic conflicts. In more severe cases, limit-setting may require removal from the home or arrests for illegal behaviors.

9) Define oppositional defiant disorder, distinguish it from conduct disorder, and describe common comorbid conditions (ADHD, learning disorder, communication disorder) which might be missed by teachers (in contrast to the more obvious behavioral problems).

- **Oppositional defiant disorder**
    - negative, hostile, and defiant to an extent greater than typically would be observed in individuals at that development stage; lasting 6 mo. or more during which 4 or more of the following are present:
        - often loses temper
        - often argues with adults
        - often actively defies or refuses to comply with adults' requests or rules
        - often deliberately annoys people
        - often blames others for his or her mistakes or misbehaviors
        - is often touchy or easily annoyed by others
        - is often angry or resentful
        - is often spiteful or vindictive
    - In contrast to conduct disorder, ODD patients don't engage in behavior that violates either the rights of others or societal norms, however, in many cases it progresses to conduct disorder
    - 93% having ODD as described by teachers also had ADHD
    - Common comorbid conditions w/ ADHD, learning disorder, communication disorder but the oppositional behaviors may be more obvious to teachers or family

10) Distinguish between intellectual disability (mental retardation) and more specific learning, communication, and motor skills disorders.

- Mental retardation (MR) or intellectual disability (ID) is a descriptive term for subaverage intelligence and impaired adaptive functioning arising in the developmental period (< 18 y). MR/ID and other neurodevelopmental disabilities are seen often in a general pediatric practice. Would probably include **deficits in learning, motor skills, and communication all at once.**
- Learning disorders involve impairments in the learning of **academic** skills, especially reading, arithmetic, and expressive writing ("dyslexia")
- Motor skills disorder describes difficulty with physical coordination
- Communication disorders involve problems with speech and language— specifically, expressive language, mixed receptive

and expressive language, stuttering, and phonological production (articulation)

11) Define pica, rumination disorder, encopresis, and enuresis, and list the most common contributory causes for these conditions and available treatments

- **Pica**
  - persistent eating of non-nutritive substances for at least 1 month
  - Poverty, neglect, lack of parental supervision, and developmental delay all can increase the risk for developing the condition
  - – Causes • Sometimes a/w MR • Vitamin/mineral deficiencies sometimes contribute, but usually no specific biological abnormalities found
  - Treatment: address medical complications (e.g. Lead paint) and psychosocial stressors; behavior therapy

- **Rumination disorder**
  - is the repeated regurgitation and rechewing of food by an infant or child, food is either ejected from mouth or reswallowed, seen in infants but also the mentally retarded
  - Lack of stimulation, neglect, stressful life situations, and problems in the parent–child relationship are risk factors for the condition to develop but are not invariably seen in all cases (similar risk factors as Pica)
  - Treatment: Address medical complications (and check for gastroesophageal reflux or hiatal hernia) and psychosocial stressors; aversive behavioral therapy (e.g. lemon juice with rumination)

- **Encopresis**
  - the repeated passage of feces into inappropriate places, either intentionally or involuntarily (considered pathological after age 4)
  - Often related to constipation, impaction, or retention w/ overflow incontinence
  - May be related to physiologic factors (ineffective sphincter control, dehydration, medication side effect) and/or psychological factors (anxiety or oppositionality) leading to avoidance of defecation
  - Complicated by anal fissures, pain ==> further retention
  - Treat constipation; behavior therapy; family therapy
  - http://www.youtube.com/watch?v=w6C9RBMCJOY

- **Enuresis**
  - the repeated voiding of urine during the day or at night into bed or clothes, either intentionally or involuntarily (at least 2x per week for 3 mos with age at least 5)
  - Often self-limited and prevalance decreases w/ age
  - Related to maturational delay; strong genetic component (family and twin studies); Insufficient nocturnal ADH secretion in some patients
  - In cases where a previously continent child becomes enuretic, a psychosocial precipitant may play a role(e.g. the birth of a sibling, hospitalization, or parental divorce)
  - Treatment: May not be necessary
  - • Assess for medical cause (especially urinary tract infection or obstruction)
  - • Behavioral strategies (preferred):
  - – Restricting fluids before bedtime, waking the child to void before enuresis can occur, and rewarding the child for staying dry overnight.
  - – Bell or buzzer attached to a moisture-sensitive pad
  - • Pharmacotherapy in severe cases or for sleepovers.
  - – TCAs (especially imipramine): relapse typically occurs and risk of side effects (especially cardiac); Desmopressin (ADH analogue)

12) A 16 year-old presents along with his mother for depression that meets the clinical criteria for major depressive disorder. You decide to prescribe an antidepressant. Describe what you would educate him and his mother about with regard to whether there is a risk of worsening suicidal ideation. [This is from the Mood Disorder Handout, pages 32-35]

- greater risk for first few months (4% vs 2% in one study, but no actual suicides)

- FDA placed black box warnings on anti-depressants due to a chance of increased suicidal risk

"Shortly after the FDA required that additional "black box" warnings (about the possibility of antidepressants triggering suicidal thinking or behavior in children) be added to labels of all antidepressants in October 2004, the FDA also required that such a warning be added to atomoxiten, despite a dearth of any data to this effect."

That was STUPID LONG fa sho!!!! :)))))))))

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Sylvius Challenge II
Mary Kate Worden, PhD
Wednesday May 4, 2011 9:10-10:00 am

Before class:
Review LOs from Central control of autonomics, Central control of eye movements, Brainstem, Hemispheric Lateralization, Language, Seizure
Review images in Sylvius software

During class:
Attendance: not required. This is an optional review session. Bring your clicker. No laptops or notes allowed. Powerpoint from this active learning exercise will be posted after class.

1. Given a lesion in the motor and/or sensory pathways, predict the signs and symptoms in the patient.

2. Given the signs and symptoms of motor and/or sensory dysfunction in a patient, localize, levelize and lateralize the lesion.

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Cortical organization and cortical deficits
Mary Kate Worden PhD and Nassima Ait-Daoud Tiouririne MD
Wednesday May 4, 2011 10:10-11:30 am

Handout and preliminary ppt are posted to class website. The final version of the ppt will be posted after class.

1. Identify the major inputs to the association cortices from other cortical and subcortical structures. Identify the major outputs from the association cortex.

Association Cortex	
Inputs	**Outputs**
1. Other cortical regions, both ipsilateral and contralateral, into layers I through V. 2. **Thalamus** (primarily the pulvinar, lateral posterior and medial dorsal nucleus). These structures relay info that is already processed into the cortex. Thalamic inputs synapse in **layer IV**. 3. **Brainstem** and **basal forebrain**. Inputs are to all layers.	1. Other cortical regions, both ipsilateral and contralateral, from layers II and III. 2. **Thalamus** (primarily the pulvinar, lateral posterior and medial dorsal nucleus). Thalamic outputs are from **layer VI**. 3. The **caudate, putamen**, and **cerebellum**, from layer V.

*Association cortices have reciprocal connections with the primary motor and primary sensory cortices.
anyone still have the merge cell feature showing on your screen? nope. Copy and paste from excel maybe? at least from Word, it hasn't worked (copy/paste) for me in the past. No big deal, I suppose. Copy/paste from excel didn't work.

2. Define the following clinical terms that describe dysfunction of association cortex: abulia, agnosia, prosopagnosia, apraxia, aphasia, agraphia, akinesia, perseveration, contralateral neglect. Recognize these features in a patient.
Terms that refer to disorders of cortical processing:

- Abulia = "non-will" ("boule" = "will" in greek)
    - loss of will or motivation
    - head injury to anterior cingulate gyrus
- Agnosia: inability to recognize categories of objects or faces, inability to identify objects using the senses
    - Visual agnosia, Auditory agnosia, etc
- Prosopagnosia: inability to recognize specific faces c
- Apraxia: loss of ability to execute learned motor movement
    - (higher-order movement, like "move your hand as though you're striking a match")
    - these patients can still read, so get them to read something like "close your eyes"
- Aphasia = "without utterance"
    - inability to comprehend and/or produce language
- Agraphia = "without writing"
    - inability to write, regardless of the ability to read
- Akinesia = "without kinesis = movement"
    - loss of spontaneous activity (sometimes characterized as staring into space)
- Perseveration: a behavior in which the patient constantly repeats the same action, whether or not it is appropriate
- Contralateral neglect: an inability to attend to objects, or even one's own body, in a portion of space, despite the fact that visual acuity, somatic sensation and motor ability remain intact.

3. Describe "neurophysiological individuality" as related to the cerebral cortex.
In general, as the information encoded in the cerebral cortex becomes more complex, individual variation in the encoding process becomes more significant. This "neurophysiological individuality" is an emergent property which itself has several important consequences:

- First, it may share important similarities with the individuality we observe in overt behavior.
- Second, this individual variability may prevent us from filling in all areas of the cortical map with identical functions for all individuals. Each person's map is probably slightly different.

- Third, it may help to explain the variability of neuropsychological deficits seen after lesions to the cerebral cortex.

4. Describe how experience can induce brain reorganization.
Experience can induce reorganization in the human brain. For example, Elbert et al found that the cortical representation of digits of the left hand, as measured by magnetic source localization, was larger in string instrument players than in controls. The degree of increase was larger in those who had begun to play prior to age 12. They concluded that the experience of string playing produced the increase in cortical representation, and that the younger brain is more plastic in this respect. A second possible explanation of the findings is that people with larger cortical representations are more likely to become string players but, based on animal studies of changes in cortical representations, this is less likely.

5. Describe the concept of lateralization and give three examples. Lateralization: Many complex functions demonstrate lateralization to one hemisphere. Examples include:

1. **Handedness.** Almost all people perform the most complex hand functions, such as eating, writing, and drawing, on one side only. But simple movements of the hands can be performed with near equal facility using either hand. Actually, precise neuropsychological testing will reveal that even the simpler movements can be done better with the "dominant" hand. For example, finger tapping speed is usually faster with the dominant hand. The more complex the motor activity, the more the nondominant hand falls behind its dominant mate.
2. **Language**. Both the receptive and expressive aspects of language are lateralized to the left hemisphere in almost all right-handers and more than half of all left-handers. The cadence and inflection of speech are usually encoded in the right hemisphere.
3. Stephan et al (2003) used BOLD (blood oxygen-level dependent) fMRI (functional Magnetic Resonance Imaging) to show that the same visual stimulus will activate different hemispheres based on the task required of the subject.
    a. Task: Do you see the letter “A” in the word “bAth?” Activation occurs in Broca’s area (in the inferior frontal gyrus) and other left hemisphere regions.
    b. Task: Is the capitalized letter in “bAth”on the left or right side of the word as you look at it? Activation occurs in the right parietal region, regardless of the position of the capitalized letter in the word.

    The visual cortex was activated bilaterally in both task conditions.

6. Compare and contrast the 3 main association areas, including their functions and related clinical deficits.
Association Areas: The most complex of central nervous system functions are assigned to the three main areas of association cortex. These areas develop last and are the first to be affected by degenerative disorders such as Alzheimer's disease. They subserve the most complex of human behaviors.

1. The **temporoparietal** association areas:
    - language, attention, and complex sensory analysis, including recognition

Representative clinical syndromes include:

a. Involving the left side
    - 1) **Wernicke's aphasia**. *Comprehension* of language is impaired. Speech is fluent, but words are misused and naming is impaired. The patient is often unaware of the deficit.
    - 2) Gerstmann's syndrome
        - left-right confusion
        - finger agnosia
        - dysgraphia
        - dyscalculia (bad at math)

b. Involving the right side
    - Deficit in nonsyntactic language (the ability to perceive and project emotional tone)
    - Neglect of the left half of the body
    - Constructional apraxia (inability to copy figures)

2. The **frontal** association areas:
    - cognition, planning, and complex motor behavior
    - Five frontal lobe systems have been delineated which have different functions and operate in parallel to each other (Duffy, 1994; Mega, 1994). They are described below (LO #7).

[Note: the orbitofrontal system, although physically in the frontal lobe and listed below as one of the five frontal lobe systems, is

considered to be part of the limbic association cortex.]

3. The **limbic** association areas:

- memory and emotion

a. Orbitofrontal cortex. [see below table]

b. Temporal lobe portion of the limbic association cortex subserves memory

7. Within the frontal association areas, list the five major subsystems, their functions and related clinical deficits.

Frontal Lobe System	Functions	Clinical Deficits
Supplementary motor	motor sequence programming; bilateral coordination.	1. disorders of initiation and control of movement. 2. disorders of posture.
Frontal eye fields	oculomotor; smooth pursuit and saccadic movements.	1. transient gaze paralysis. 2. impaired predictive saccades. - these patients look toward the side of the lesion
Dorsal convexity (dorsolateral prefrontal)	executive cognition. organization of complex tasks.	1. poor organization of behavior, especially in response to novel problems. 2. poor working memory. 3. poor performance on delayed response tasks.
Orbitofrontal (part of limbic association cortex)	personality; socially appropriate behavior. critical restraint and empathy.	1. disinhibition 2. aggression 3. impulsivity 4. poor response to social cues
Mesial frontal (anterior cingulate)	motivation. exploration.	1. apathy 2. poverty of spontaneous speech; mutism 3. indifference to surroundings

Mnemonics:
Supplementary motor = deficits remind me of Parkinson's.
Orbitofrontal = deficits remind me of antisocial personality disorder.
Mesial frontal = deficits remind me of schizoid personality disorder. (or too long in MBB)
Frontal eye fields = LEFT hemisphere contains the RIGHT visual field, and vice-versa. So if a left-sided lesion, right visual field is gone -> looks to the left.
I think instead of visual fields it would be better to think of the L cortex projecting to the R PPRF which controls rightward gaze. If the L cortex goes, there is no rightward gaze and thus eyes deviate to the L, the side of the lesion.
Frontal Eye field lesion (in the brain) = too interesting to look away (frontal lobes also involved in exploration, etc)
PPRF (in the brainstem) = too devastating to look at (brainstem lesions cause many neighboring signs, up to death)
Guys, are we sure about this? The Sylvius challenge lists damage to the frontal lobe as 'Patient will gaze AWAY from the side of the lesion'
It's probably a mistake in the Sylvius Challenge then, given that other internal and external sources confirm that damage to the frontal eye fields will cause the eyes to deviate towards the side of the lesion. If the lesion extended further caudally, the patient would experience contralateral hemiplegia (so the patient would gaze away from the side of the hemiplegia).

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Psychological Testing
Bruce Cohen, MD
Self-study

Review/read:
1. Theory and Practice of Psychiatry. Chapter 2: Psychological Testing pp 43-46
Note: there is a mistake in Table 2-10 in that the WAIS and the WISC are reversed. The WISC is for ages 6-16 and the WAIS is for 16-adult)
2. Look at photos of the 10 Rorschach inkblots on http://en.wikipedia.org/wiki/Rorschach_inkblot_test#The_ten_inkblots
3. Look at "Sample MMPI report" on the course website. (Don't spend much time on this, it's simply meant to give an example of how the patient spends 1-2 hours answering 567 True-False questions and these questions fall into different scales. Based on the responses within each scale, one can construct a bell-curve for the general population (or some other specific population, e.g. college students, plaintiffs in personal injury suits, prison inmates etc) and then see for each scale where the patient falls relative to this population. One can look at the overall pattern (high in some traits, average in others, low in yet others) and get an overall sense of personality. However, it's not a substitute for a clinical exam, it just supplements the exam and one needs to be cautious in how one interprets a given profile.

1) Describe the goals of psychological testing and the difference between cognitive tests and personality tests
- adjunct to psych history and mental status exam
- standardizes assessment and compares pts to a normative population
- provides objectivity
- can assess broad range of attitudes and aptitudes over short range of time
- particularly useful in difficult dx situations (e.g. distinguishing dementia due to closed head injury sustained during a motor vehicle accident from feigned cognitive complaints motivated by hopes of winning a large financial settlement)
- useful in psych research

Cognitive tests: measures particular skills, aptitudes, and academic performance; designed to measure pt's best performance
Ex: Wechsler Adult Intelligence Scale (WAIS) IQ test

Personality: measures long-standing personality characteristics (like histrionic, hypochondriacal) OR current psychological symptoms (like depression, anxiety, anger)
Ex: Minnesota Multiphasic Personality Inventory–2 (MMPI-2) - 576 standardized true/false questions (e.g. "I have used alcohol excessively")

2) Within cognitive tests, describe the difference among IQ tests, achievement tests, and neuropsychological tests. Describe what one pattern of mismatch between IQ testing and achievement testing one might see in a case of learning disability (e.g. a person who has difficulty specifically with reading skills or math skills).
- **IQ tests:** combine both verbal tasks and performance tasks (more abstract thinking; also visual-motor coordination, etc) into an assessment of overall performance that is weighed against the general population. The population results are standardized such that the mean score is 100
    - IQ tests are said to correlate with overall academic performance
    - Verbal tasks measure the fund of general information, word knowledge, verbal reasoning, social judgement, arithmetic skills, and number recall.
    - Performance tasks measure visual recognition, temporal sequencing, visual-constructive skills for familiar objects & abstract designs, and speed of visual-motor coordination.
- **Achievement tests**: specifically assesses academic skills such as reading, writing, math etc
    - Achievement tests may show areas of weakness, such that, when weighed against the person's IQ/age/school level, the achievement test may offer insight into a learning disorder (e.g. reading or mathematics disorder)
- **Neuropsychological tests:** assess for impairments in specific areas of cognitive functioning (attention, concentration, verbal fluency, memory, abstract reasoning, problem solving, mental flexibility, speed of information processing, sensory & motor

function); commonly used in setting of brain injury
    - Such information can aid the clinician both in clarifying the patient's diagnosis and in identifying areas of relative strength and vulnerability, thereby facilitating treatment planning and assessment of the patient's need for additional community or educational supports

In people with learning disabilities, one may have a normal IQ score (reasoning and problem-solving abilities), but concurrent poor achievement testing in **specific** areas (e.g. reading or math) that are not directly assessed in an IQ test [[somebody please check this]] *"While intelligence is closely correlated with academic performance, **achievement tests** more specifically assess academic skills such as reading, mathematics, and written expression. When these skills fall substantially below what would be expected for the patient's age group, level of schooling, and level of intelligence, a learning disorder (e.g., a reading disorder or mathematics disorder) might be diagnosed."* I read that as - normalized for the patient's respective IQ, age, and level of schooling, when a patient performs substantially below his overall normalized group in a specific academic skill (or the group of skills), a learning disorder may be diagnosed. I've edited the above points to reflect this. You are awesome.

3) Within personality tests and symptom severity measures, describe the difference among objective tests, projective tests, and semistructured interview measures.

- **Objective:** very structured tests, like the Minnesota Multiphasic Personality Inventory-2 and Beck Depression Inventory-2; self report inventories, in which the individual being tested reads the items and selects the option (T/F or MC) that is the best self description; use a computer to analyze hundreds of T/F or MC answers to questions
- **Projective:** unstructured; pts asked to describe what they see (like with Rorschach inkblots, or with cards where patients are asked to create a story of what a particular picture may be depicting); assess unconscious aspects of personality
    - Two different individuals will choose to structure such unstructured stimuli in their own characteristic ways; How they do so often reveals something about their self-image, their affective style, their prominent areas of concern, how organized they are in their thinking, and how they perceive interpersonal relationships.
- **Semi-structured:** similar to normal clinical interview, but questions (and follow up questions) are standardized; clinician uses judgement to determine if symptoms present
    - ensure reliable diagnostic practice; used primarily in research studies

4) Describe how a general medical practice might use self-report measures and checklists either to screen for the presence of psychiatric illness (e.g., using a form that all new patients complete in the waiting room along with their medical history, insurance information, etc) or to measure in a more reliable and quantitative fashion a patient's response over time to treatment (e.g., giving a patient with depression a Beck Depression Inventory to fill out at each visit).

- This is not from the book, but it seems logical that clinicians could try a shortened list of questions to assess psychological state (like the MMPI-2, but for efficient), sort of like cancer centers do with "stress thermostat" assessments; I can't speak for others. As said in the LO, changes in their responses over time may offer insight
- I think the answer is in the LO itself

5) Describe which tests might prove to be the most useful in trying to sort out a complicated case of medication-refractory depression where the patient might have an intellectual disability and/or a personality disorder complicating the diagnostic picture.

My guess is you would use any of the available tests to clarify the presence or absence of either an intellectual disability or a personality disorder, so for example:
- For an intellectual disability: WAIS-III (an intelligence test), or WRAT-3 (an achievement test)
- For a personality disorder: MMPI-2 (an objective personality test), or the Rorschach test (a projective test)
You would then use the information gleaned from these tests, combined with any insights you've gained from the H&P, to assess the presence of an intellectual disability and/or a personality disorder that could complicate the diagnostic picture of an already-complicated patient with medication-refractory depression.

Emailed Dr. Cohen to see what's up. His response: "All of the below [referring to current answers to LOs#5-6] are correct!"

6) Describe which test battery might be useful in assessing an individual who sustained a head injury in a motor vehicle accident, and what information might be gained from this testing compared to relying only on the clinical interview and physical examination.

- Likely a neuropsychological test battery (assessing attention, concentration, verbal fluency, memory, abstract reasoning,problem solving, mental flexibility, speed of information processing, sensory & motor function that are subject to change with brain injury) would be useful as an adjunct to clinical interview and physical exam.

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Brain Death and Consciousness Disorders
Bart Nathan, MD
Thursday May 5th, 2011, 08:10am-09:00am

Blumenfeld:
Locked-in Syndrome Chapter 14: KCC 14.1 pg. 625
The Consciousness System Chapter 14: pgs. 627-636
Coma and related disorders: Chapter 14: KCC 14.2 pgs. 640-646
Coma Exam Chapter 3 pgs. 74-79
Brain Death Chapter 3 pg. 79

Learning objectives (before class):
1. Define and describe the differences of the following terms: locked in state, coma, brain death, vegetative state, persistent vegetative state, minimally conscious state.
- **Locked in state** - patients with absent motor function, but intact sensory and cognitive function (resembles a coma, but patient retains ability to engage in vertical eye movements and blinking)
    - Usually due to infarct in ventral pons affecting bilateral corticospinal & corticobulbar tracts
    - Sensory pathways & brainstem reticular activating system are spared ⇒ patient is thus fully aware, able to hear, feel, understand
    - Vertical eye movements are spared b/c they are controlled by the riMLF (in the tegmentum of the rostral midbrain)
        - Horizontal eye movements are affected b/c they depend on pontine circuits (PPRF)
        - However, conjugate gaze (adduction on both sides) would be intact, just harder to test
- **Coma** - unarousable unresponsiveness in which the patient lies with eyes closed
    - unlike w/ brain death, during coma many simple or even complex reflexes can occur (e.g. VOR, posturing, intermittent stereotyped spontaneous movements, **reflexive (**but NOT purposeful) withdrawal from noxious stimuli)
    - "unresponsiveness" refers to absence of psychologically meaningful or **purposeful** responses that are mediated by the cortex
    - EEG can show many different patterns, but is typically monotonous w/ little variability over time (unlike the normally varying EEG seen during sleep)
    - Cerebral metabolism reduced by at least 50%
- **Brain death** - **irreversible lack of brain function** (from a known cause); extreme form of coma in which clinical exam shows no evidence of forebrain or brainstem function (no brainstem reflexes), EEG shows brain inactivity, and cerebral metabolism and perfusion are reduced to 0
- **Vegetative state** - period following coma in which patient regains sleep-wake cycles, primitive orienting responses, and reflexes mediated by the brainstem and hypothalamus, but remains unconscious
    - open their eyes and arouse in response to stimulation, may turn head toward auditory/tactile stimuli
    - may produce unintelligable sounds and move their limbs but do not have meaningful speech/gestures
- **Persistent vegetative state** - vegatative state described above lasting > 1 month
    - as in coma, no purposeful responses to stimuli, >50% reduction in cerebral metabolism indicating diffuse cortical dysfunction
    - unlike w/ coma, patients in PVS open their eyes and arouse in response to stimulation (via brainstem-mediated pathways)
- **Minimally conscious state -** can occur as further stage of recovery from vegetative state; minimal degree of responsiveness- can track visual objects, follow simple commands, say single words, or reach for /hold objects; no reliable interactive verbal or non-verbal communication & no reliable functional use of objects

	Cerebral cortex: *Purposeful response to stimuli*	**Diencephalon/upper brainstem arousal:** *Behavioral arousal, sleep-wake cycles*	**Brainstem reflex & motor systems:** *Brainstem reflexes?*	**Spinal cord circuits:** *Spinal cord reflexes?*
Brain death	No	No	No	Yes
Coma	No	No	Yes	Yes
Vegetative State	No	Yes	Yes	Yes
Stupor, lethargy, delirium	Yes (at times)	Yes	Yes	Yes
Sleep	Yes (at times)	Yes	Yes	Yes
Status epilepticus	Variable	Variable	Yes	Yes
Locked-in syndrome	No	Yes	Yes	Yes

2. Explain why maintenance of the normal awake state does not depend on a single projection system
The awake state can be considered to be controlled by a collection of "diffuse projection systems" which emanate from a single region to innervate many structures or even the entire CNS. These widespread projection systems are seen in the control of alert consciousness, attention, the sleep-wake cycle, and emotional balance.

3. Describe the effect of pharmacological blockade of the cholinergic transmission in the CNS.
Pharmacological blockade of central cholinergic transmission causes delirium and memory deficits.

- The main roles of acetylcholine in the CNS are facilitation of attention, memory, and learning

4. Explain the role of noradrenergic agents in attention deficit disorder and narcolepsy.
Functions of the ascending noradrenergic projection system (project from the locus ceruleus & lateral tegmental area in the pons & medulla to the entire forebrain) include modulation of attention, sleep-wake cycles, and mood.

- Firing of the locus ceruleus neurons increases in the awake state & decreases during sleep.
- ADHD and narcolepsy are often treated with medications that enhance noradrenergic transmission.

5. Explain the proposed role of the serotonergic system in the pathophysiology of sudden infant death syndrome.
5-HT normally helps babies respond to high carbon-dioxide levels during sleep by helping them wake up and shift their head position to get fresh air. Compared with controls, infants that died due to SIDS had lower levels of 5-HT in their brainstems (source: http://www.ncbi.nlm.nih.gov/pubmed/20124538)

- Like noradrenergic neurons, serotonergic neurons markedly decrease their firing rate during sleep and are likely involved in arousal.
- Deficits in serotonin neurons => risk of **sudden infant death syndrome (SIDS)**, possibly caused by impaired arousal in response to hypoventilation

6. Explain how anti-histaminergic drugs can cause drowsiness.
Histaminergic neurons of the tuberomammillary nucleus in the posterior hypothalamus participate in a circuit with the hypothalamus that regulates sleep and arousal

- Histaminergic projections from the tuberomammillary nucleus to the forebrain may be important for maintaining the alert state
    - Histamine has excitatory effects on thalamic neurons
- Inhibitory neurons projecting to the tuberomammillary nucleus that inhibit histamine release promote deep sleep. This same effect can be seen with drugs that perform the same function.
    - Benadryl = H1 receptor antagonist => drowsiness

7. Name the 3 principle processes of consciousness.
Mnemonic: "AAA"

1. Alertness

2. Attention
3. Awareness

8. Name the 3 regions of the brain that may be dysfunctional in coma. State whether damage to one or two cerebral hemispheres are sufficient to cause coma.

Classically, coma is caused by dysfunction of:

1. Upper brainstem reticular formation (lesions to other portions of the brainstem do not generally result in loss of consciousness)
2. Extensive bilateral regions of cerebral cortex
3. Bilateral regions of the thalamus

9. Describe the 3 most common causes of coma localized to the cerebral hemispheres. List the 2 most common causes of coma localized to the brainstem.

- Coma localized to cerebral hemispheres: global anoxia, other **toxic/metabolic disorders**, head trauma; also: bilateral ischemic infarcts
- Localized to brainstem: extrinsic compression from cerebellar/cerebral mass lesions or intrinsic brainstem lesions (infarct/hemorrhage)

10. Explain why it is better to describe the patient's neurologic exam rather than use the terms stupor, lethargy, obtundation or semicoma.

Terms like stupor, lethargy, obtundation, and semicoma are poorly defined terms used sometimes to describe patients on a continuum from coma → fully awake.

- Use of these terms alone, without further detail, can be confusing to other physicians. Therefore, specific statements of what the patient did in response to certain stimuli is preferred (e.g. "upon application of deep pressure to the patient's nail bed, he opened his eyes and moaned").

11. State why coma is a neurological emergency. List the 3 things that should emergently be administered intravenously when a patient presents in coma. Be able to describe a simple diagnostic workup of a patient who presents in coma.

Coma is a neurological emergency because many causes are reversible, but can cause permanent damage that increases in severity over time if not treated. 3 important first tasks:

1. IV thiamine (thiamine deficiency, Wernicke Korsakoff)
2. IV dextrose (hypoglycemia)
3. IV naloxone (opiate overdose)

   Give these **before laboratory results are obtained** to combat readily treatable causes of coma.

- A typical coma work up might include:
  - pupil sizes and responsiveness (see LO #12), blood tests (looking for toxic/metabolic causes), head CT (looking for potential need for neurosurgical intervention, e.g. cerebrovascular trauma or brain herniation), LP to check CSF (if head CT has excluded the danger of herniation and cause still unknown), EEG (if cause is unknown, to check for subtle status epilepticus).

12. Describe 4 typical pupillary abnormalities in coma

1. Normal-sized, reactive pupils → consider toxic/metabolic causes of coma first
   a. suggests cortical coma
2. Unilaterally or bilaterally-dilated ("blown"), unresponsive pupils → consider midbrain compression and transtentorial herniation first
3. Bilateral small but responsive pupils → consider pontine lesion first
4. Bilateral pinpoint pupils → consider opiate overdose first

13. Be able to describe the general outline of the examination of a comatose patient (ie. What can be tested and what cannot)

- Mental Status
  - Document level of consciousness with a specific statement of what the patient did in response to particular stimuli
- Cranial Nerves
  - Ophthalmoscope exam (CN II)- look for papilledema which indicates increased ICP

    - Vision (CN II) – blink to threat (rough estimate of visual fields)
    - Pupillary responses (CN II, III, sympathetics)
    - Extraocular Movements and VOR (CN III, IV, VI, VIII)
        - Spontaneous extraocular movements
        - Nystagmus
        - Disconjugate gaze
        - Oculocephalic maneuver
            - if in coma, eyes will move relative to the head (as if eyes stayed focused on image in front). This is, of course, assuming that the vestibular, abducens, and oculomotor nuclei are not messed up
                - absence of this reflex in comatose patients indicates brainstem dysfunction
            - note: reflex is not usually present in awake patients because voluntary eye movements will mask the reflex (i.e. in awake patients eyes will NOT move relative to the head in the smooth sense; will probably look around like WTF mate (random plug: http://www.endofworld.net/))
        - Caloric testing
    - Corneal reflex, facial asymmetry, grimace response (CN V, VII)
        - look for facial asymmetry at rest or asymmetrical spontaneous blinking or grimacing
        - facial grimacing should be observed in response to pain or firm pressure applied to each orbital ridge
    - Gag reflex (CN IX, X)
- Sensory and Motor Exam
    - Spontaneous movements
        - no purposeful movements (mediated by cortex) will occur in a comatose patient
    - Withdrawal from painful stimuli
        - this will not occur in a comatose patient
        - distinguish **purposeful** withdrawal from **posturing reflexes**
            - e.g. in decorticate posturing, arm will flex even when flexor side of the arm is pinched, moving toward the painful stimulus. In purposeful withdrawal, movement is away from the stimulus.
- Reflexes
    - Deep tendon reflexes
        - should be present
    - Plantar response
        - may or may not be present
    - Posturing reflexes: decorticate or decerebrate
        - may be present
    - Special reflexes (in case of suspected spinal cord lesion)
- Coordination and gait – usually not testable

14. Name two criteria that, when both are met, indicate brain death.

1. Clinical examination demonstrating no evidence of brain functioning, including the brainstem and forebrain, including no brainstem reflexes
2. Caloric testing and apnea test (patient will lack spontaneous respirations w/out ventilator, despite changes in blood pH or pCO2)

- In US, patient with posturing reflexes involving the brainstem does not meet criteria for brain death, but a patient with only triple flexion and deep tendon reflexes may
- Reversible causes must be tested for, if part of evaluation is inconclusive use ancillary tests such as angiogram or EEG (confirmatory only)

15. Explain whether a diagnosis of brain death is consistent with the presence of peripheral nervous system activity and spinal cord reflexes

- Yes, spinal cord reflexes may be present
    - You cannot have any brain activity, but you can have peripheral or spinal cord reflexes and still be brain dead.

During class:

1. List the tests for brainstem function that should be performed before diagnosing brain death.

- Cranial nerve function:
    - Pupils medium, symmetric, and unreactive
    - When head moved, eyes won't move relative to the head (they will move with the head)
    - No response to water in the ear
    - Pushing on the supraorbital area does nothing
    - Gag reflex gone
    - No blinks to threat
    - Sternal rub does nothing
    - No posturing (no decorticate or decerebrate)
    - Squeeze fingers -> nothing (= no response to pain in extremities)
    - Deep tendon reflexes can be intact (since mediated by spinal cord); Babinski may be present
- Apnea test - d/c the pt. from the ventilator and see if they breathe (have to be cardiopulmonary stable & not be in shock)
    - you will see no reaction
- Confirmatory tests (e.g. EEG, angiogram) as needed if you can't do the other tests
    - flat EEG
    - lack of blood flow (especially clear when using contrast) to cortex

Time of death = when you declare them dead by neurologic criteria (not when you turn off the ventilator, or when the heart stops)

2. Explain how a diagnosis of brain death can be confounded by each of the following complicating medical conditions: drug and metabolic intoxication, hypothermia, shock.

- Brain death = irreversible lack of brain function due to a known cause
    - Some causes: Anoxic injury, uncal herniation
- Reversible causes: drug (barbiturates and BDZs) and metabolic intoxication (liver failure), hypothermia, shock
    - These can mimic the signs of brain death but are reversible
    - Hypothermia: patient will not have brainstem reflexes & won't breathe

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Eating Disorders
Bruce Cohen, MD
Thursday May 5, 2011 9:10-10:00 AM

Before class:
Required:
1) Theory and Practice of Psychiatry. Chapter 11: Eating Disorders pp 318-338.
(Also, If you want to read a detailed vignette involving anorexia and see how I formulate it from all four perspectives, you can review pp. 50-53).

2) Eating Disorders supplemental handout (on course website);
a) I have provided updated information on pharmacotherapy of eating disorder (primarily a 2006 study involving fluoxetine in anorexia and some further information on use of atypical antipsychotic medications in anorexia) and bullet points about the stages of treatment (however, the chapter covers these in greater detail and more clearly);

b) I have provided tables related to assessment and management of medical complications in anorexia and bulimia. You should review these as a supplement for better understanding when approaching learning objective #6 and #7b, but do not memorize the tables!

3) Look at this website: http://en.wikipedia.org/wiki/Pro-ana . Questions to think about in looking at this website:
a) As with other conditions (including substance abuse, paraphilias, somatoform disorders, dissociative disorders, and also conditions such as "adult ADHD," "mild Aspergers" disorder and even cigarette smoking), how does whether the surrounding community chooses to support or criticize an individual facilitate or discourage the initiation and/or perpetuation of a behavioral disorder?

b) How might similar factors play out in a self-help therapy group for individuals with eating disorder as opposed to a therapy group that is directed by a therapist who doesn't have eating disorder?

c) How might similar factors play out in a longer-term (several week stay) inpatient eating disorders program where all of the patients room together, eat together, discuss the staff together, etc?

d) Finally, to what extent has the Internet helped to provide useful education about eating disorder vs. spread advice and encouragement from other affected individuals (who in the past suffered alone) that actually encourages the development of more eating disorder?

4) Look at this article: http://www.nytimes.com/2010/10/19/health/research/19anorexia.html and consider these questions:
a) This, along with inpatient treatment appear to be the most effective treatment available for anorexia. However, inpatient treatment removes the patient from her life for many weeks, is very expensive (and often insurance companies won't pay it), and the post-discharge relapse rate is high. How practical is this intensive outpatient approach for most families in terms of the time commitment involved?

b) Would this approach work for all families where a child has an eating disorder? What if family interpersonal conflict has been a longstanding major difficulty beyond conflicts over food?

Learning objectives:
1) Describe the clinical phenomenology of eating disorder, including the DSM-IV symptoms of anorexia nervosa and of bulimia nervosa and the two subtypes of each of these diagnoses. Define a "binge."
Describe the phases of a binging episode (appetitive/craving; consummation, satiety, followed by compensatory behavior).

- DSM-IV **Anorexia Nervosa**
    - Refusal to maintain body weight at or above a minimally normal body weight for age and height (e.g. weight loss

leading to maintenance of body weight less than 85% of that expected; failure to make expected weight gain during period of growth leading to body weight less than 85% of that expected
    - Intense fear of gaining weight or becoming fat, even though underweight
    - Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousnsess of the current low body weight
    - In post menarcheal females, **amenorrhea** (absence of at least 3 consecutive periods)
    - 2 Subtypes
        - **Restricting Type**: No binge-eating or purging behavior during current episode of anorexia
        - **Binge-Eating/Purging**: Regularly engages in binge-eating or purging behavior during current episode of anorexia
- DSM-IV **Bulimia Nervosa**
    - Recurrent episodes of binge eating; an episode of binge eating is characterized by both of the following:
        - Eating in a discrete period of time (e.g. within any 2-hour period) an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
        - A sense of lack of control over eating during the episode (a feeling that one cannot stop eating or control what or how much one is eating)
    - Recurrent inappropriate compensatory behavior in order to prevent weight gain (self-induced vomiting, misuse of laxatives, diuretics, enemas, other medications, fasting, excessive exercise)
    - Binge eating and inappropriate compensatory behaviors both, on average, **cycle at least twice a week** for three months
    - Self-evaluation is unduly influenced by body shape and weight
    - Doesn't occur exclusively during episodes of anorexia nervosa
    - Two subtypes
        - **Purging**: During the current episode, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas
        - **Nonpurging**: During the current episode, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly used the above methods

2) Describe how eating disorder can be conceptualized from the disease perspective, from the dimensional perspective, from the life story perspective, and from the behavioral perspective.

- Disease - if you can find some imbalance in brain chemistry, you can treat with medication
- Life-story - if you can gain an understanding of the anorexic patient's *unconscious motivations* for starving themselves, you can assist the patient to give up maladaptive behaviors for more appropriate coping behaviors
    - Symptoms viewed as function of underlying psychological disturbances
- Behavior - views anorexia as a motivated behavior (goal-directed and designated by its consequences). Can be ignored, voluntarily suppresses
    - 3 phases
        - craving
        - consummatory behavior
        - decrease in the drive and its replacement by another activity
- Dimensional - no clear demarcation between normal behavior, problem behavior, and pathological behavior. Distinctions are socially defined and occasionally arbitrary

3) Using the behavioral perspective, describe how eating behavior (like other behaviors such as substance use, somatization, gambling, sex, shopping, Internet use, etc.) is a behavior that occurs with less-severe (non-addictive) intensity throughout the population, with a subset of the population being more vulnerable to this behavior becoming more severe with less ability to control it.

- Majority of Americans engage in dieting behavior at some point, with the goal of attaining thinness and diminishing a fear of becoming fat. =
    - In the average person, dieting is under voluntary control
    - In anorexia nervosa, the intensity of the drive becomes excessive, and it becomes completely preoccupying and self-sustaining

- Initiation of dieting behavior and initial extent of dieting can be influenced by both internal and external conditions
- Eventually, the behavior **becomes autonomous**
    - Ability to voluntarily control becomes diminished or absent
    - Secondary mechanisms play a significant role (e.g. abdominal pain and edema with attempts at refeeding)
- Eventually illness becomes the patient's identity ("I don't have anorexia; I am anorexic") and she becomes unwilling to give up that identity

4) List the major factors that predispose a vulnerable individual to develop an eating disorder, including:
a) Gender (how do men and women differ with regard to how they eat?; what factors associated with being female might account for eating disorder being 10 times more common in women than in men?; how does eating disorder present differently in men than in women?):

- Men experience hunger that is more acute, eat earlier in the day, take larger bites, and eat more rapidly than women
- Appetite in women varies over the course of the month in response to fluctuation in hormone levels (estrogen decreases, progesterone increases), while appetite in men does not
- Men's eating habits are more stable during periods of stress. When they feel overweight they are more likely to attempt to work it off through increased exercise rather than initiating a diet
- Women who feel stressed or depressed are more likely to gain weight and then feel dissatisfied with their bodies. They are **more likely to diet than to exercise**, and are more likely to rebound from a diet into overeating
- 1/3-1/2 of anorexic women stop menstruating before they start to diet or lose weight- amennorhea may be a marker of **disregulation of HPA axis causing biologic vulnerability**
- Serotonin and prolactin levels change in response to dieting in women but not in men
- Males who develop eating disorders tend to initially seek muscle definition rather than thinness, and are usually involved in athletic activities where weight is an important factor, such as wrestling
- In men who have eating disorders, higher prevalence of bisexuality or homosexuality than among women

b) Societal and cultural pressures:

- Our culture values high fat foods and thinness, which makes *tons* of sense advertising = culture valuation?
- Typical role models for girls include ballet dancers, fashion models, gymnasts, and cheerleaders, many of whom themselves have eating disorders
- In contrast to most major mental illnesses, eating disorders occur **more commonly among members of industrialized nations** and members of upper socioeconomic classes. Also more common in certain religious and ethnic groups (Jews, Italians, Catholics)
- Second generation minorities (blacks, Hispanics, Native Americans) who achieve status show increased prevalence, as do natives of Arab countries who immigrate to the West, indicating **"culture-bound" features** of the syndrome

c) Personality Vulnerabilities:

- Restricting anorexia tends to develop in women who are premorbidly perfectionistic, rigid, socially insecure, dependent, and fear autonomy
    - Many meet criteria for obsessive compulsive personality disorder and some for OCD
    - Malnutrition amplifies these traits and also causes depression
    - *the insecure, perfectionistic, dependent type (above) v. the outgoing and insane type (below)?*
- Patients who develop bulimia or the binging-purging form of anorexia are more likely to be extroverted, impulsive, and sensitive to rejection
    - Often meet criteria for borderline personality disorder
    - More likely to abuse alcohol, steal, be sexually active, attempt suicide, and have affective instability (rather than persistent depression)
    - Tend to see the world as a stressful and uncaring place, and therefore predisposed to turn to dieting for gratification
    - Rigid diet leads to **state of deprivation that they are unable to tolerate** (as opposed to restricting anorexics), leading to binge; initially experience euphoria but then severe guilt and anxiety, also intolerable, and this leads to the purge

d) Family functioning:

- Restrictive anorexia
    - Mothers of restricting anorexics most often are intrusive, dominating, overprotective, critical, socially introverted, and phobic
    - Fathers of restrictive anorexics tend to be passive, submissive, emotionally sensitive, and withdrawn, often overshadowed or belittled by his wife
    - As a couple, parents tend to be overprotective and overambitious in their expectations for their child, expecting obedience & superior performance
    - Family tends to be enmeshed and rigid, lacking skills at conflict resolution and interested in maintaining the current emotional homeostasis
    - Adolescents from these families, rather than experimenting w/ different identities & separating from parents, fear autonomy
        - Self-starvation and emaciation prevent separation and reinforces the status quo
        - Paradoxically, it also allows the anorexic to be assertive and aggressive, but in a way that minimizes separation
- Bulimia
    - Families of bulimic patients tend to be more emotionally distant, less cohesive and structured, with greater expressions of overt conflict
    - High parental expectations of child

e) <u>Dieting and exercise</u>:

- Up to 75% of anorexic women report having engaged in excessive physical activity prior to initiation of dieting
    - <u>Exercise may play a role in triggering onset</u> of eating disorder (causes release of endorphins, which suppress appetite and elevate mood)
- Vigorous exercise likely activates the same pleasure circuit implicated in substance dependence, mediated by dopamine and other neurotransmitters. Excessive exercise itself can become self-reinforcing

f) <u>Onset of puberty</u>:

- <u>Adolescence is period of greatest risk</u> for development of eating disorder
- Development and hormonal factors associated with puberty probably play a significant etiologic role
- Change in body morphology occurs during puberty - females have significant shift in fat-to-lean ratio. Body fat increases by 120% while lean mass only increases 40%

g) <u>Acute Stress</u>:

- Many patients experience onset or exacerbation of eating disorder during periods of increased stress
    - Ex. developing anorexia shortly after leaving home for first time to attend college
- Many patients create their own stress (due to perfectionism and inability to set limits) or interpret events as more stressful than other people
- Animal models show stressed animals continue eating even after should be satiated

5) Describe how the above factors (e.g. typical personality disorder comorbidity, typical family dynamic) differ between people with (a) anorexia nervosa, restricting type vs. (b) anorexia nervosa, binging/purging type and bulimia nervosa

- Personality disorder
    - Patients who develop restricting anorexia tend to be perfectionistic, rigid, socially insecure, dependent, and fear autonomy
        - Many meet criteria for obsessive compulsive personality disorder and some for OCD
        - Actively resist urge to eat
    - Patients who develop bulimia or the binging-purging form of anorexia are more likely to be extroverted, impulsive, and sensitive to rejection
        - Often meet criteria for borderline personality disorder
- Family dynamic
    - Anorexic patients are more likely to be enmeshed with their families, while bulimic patients are more likely to be alienated from their families
    - Restrictive anorexia

        - Mothers of restricting anorexics most often are intrusive, dominating, overprotective, critical, socially introverted, and phobic
        - Fathers of restrictive anorexics tend to be passive, submissive, emotionally sensitive, and withdrawn
        - As a couple, parents tend to be overprotective and overambitious in their expectations for their child
        - Family tends to be enmeshed and rigid, lacking skills at conflict resolution and interested in maintaining the current emotional homeostasis
        - Adolescents from these families fear autonomy
            - Self-starvation and emaciation prevent separation and reinforces the status quo
            - Paradoxically, it also allows the anorexic to be assertive and aggressive, but in a way that minimizes separation
    - Bulimia
        - Families of bulimic patients tend to be more emotionally distant, less cohesive and structured, with greater expressions of overt conflict
        - High parental expectations of child

6) List the major factors (a combination of positive and negative reinforcing stimuli) that <u>reinforce and perpetuate</u> the disorder once it has been initiated, including:

a) Neurophysiologic changes associated with starvation:

- Starvation causes personalities to become more obsessional, egocentric, and sarcastic when others offer help (i.e. starvation makes you act like an anorexic)
    - <u>Neurotransmitter changes make impulses more difficult to resist</u> and also contribute to depression and cognitive deficits which resolve only with weight restoration
- Structural neuroimaging studies show that <u>starvation is associated with cerebral atrophy</u> in 82% of patients with anorexia
    - Impairment typical of subcortical dementia
    - Decrease in mental flexibility and judgment may exacerbate resistance to changing maladaptive behaviors
- Functional neuroimaging reveals starvation is associated with increased caudate metabolism
    - May be associated with greater likelihood of developing compulsive or driven behaviors
- Bulimic binging and purging can lead to profound electrolyte, neurotransmitter, and endocrine changes

b) Norepinephrine:

- Important substrate for depression and anxiety (states associated with eating disorders)
- Plays a direct role in feeding behavior, influencing appetite at the hypothalamic level
    - Alpha agonists (amitriptyline and marijuana) produce hyperphagia
    - Beta agonists (cocaine and amphetamines) inhibit feeding behavior
- Starvation may lead to decreased brain NE levels, leading to decreased anxiety and decreased metabolism (protects by decreasing nutrient requirements, appears to resolve with weight gain)

c) Serotonin:

- Serotonin plays important role in OCD, researchers have suggested that eating disorders are part of an obsessive-compulsive spectrum of disorders
    - SSRIs useful in treating OCD and bulimia
- <u>Serotonin acts on ventromedial hypothalamus, triggering sensation of satiety</u> and inhibiting feeding behavior following meal. Serotonin deficiency causes extreme hunger
- Circulating levels of serotonin may be lower with malnutrition as its synthesis depends on dietary intake of tryptophan
- In anorexia SSRIs can help decrease obsessional behaviors and depression but have little effect on weight gain
- In bulimia SSRIs can increase feelings of satiety with eating, decrease cravings to binge, and decrease both depression and irritability

d) Endorphins:

- Starvation in anorexia may be accompanied by increased endorphin release
- Among bulimics, those who vomit show increased plasma beta-endorphin compared to bulimics who don't vomit
- In nondieting humans, exogenous opiate drugs increase appetite. In food-restricted animals, opiates decrease appetite
    - Can be reinforcing in both anorexia and bulimia

e) Cholecystokinin (CCK):

- No role in anorexia, but plays role in bulimia
- Release is triggered by medium-chain fatty acids and some amino acids
- CCK binds to vagal afferent nerves that lead to hypothalamus, contributing to sensation of satiety
- One theory is that bulimic individuals demonstrate blunted CCK response, decreasing feeling of satiety that normally occurs in response to food intake

f) Other factors (Neuropeptide Y and Peptide YY, Leptin, rebound hypoglycemia, cortisol levels):

- Neuropeptide Y and Peptide YY
  - PYY is most potent feeding stimulator known - levels decline shortly after meal has been ingested, contributing to satiety
  - In anorexic patients PYY levels are normal, but NPY levels are elevated
  - In bulimic patients PYY and NPY levels are normal while actively binging, but significantly increase after have ceased engaging in binging behavior (so they want to eat again)
- Leptin
  - Encoded for by gene called obese. Its receptor is coded for by a gene called diabetes. In mice, if leptin or receptor production is disrupted, this leads to obesity
    - Such gene disruptions have not been observed in humans
    - In humans (and mice), leptin levels strongly correlate with the amount of fat in a one's body
  - Altered levels in patient with eating disorder more likely to reflect patient's nutritional state rather than cause it
  - Leptin levels are very low in people with anorexia while in the starved state
    - so these people are experiencing similar levels as obese people (ones in which leptin production is impaired)? I thought obese individuals had normal levels of leptin, indicating that there was something wrong with the receptors, not the production of leptin itself?
- Rebound hypoglycemia
  - Occurs about 2 hours after binge-purge episode
  - Associated with lightheadedness, aggression, anxiety, tachycardia, and increased hunger.
  - May exacerbate binge-purge cycle
- Cortisol levels
  - Increased in bulimia
  - May contribute to carbohydrate craving and weight gain

Cohen email -> Posted in Discussions.

7) List the major medical complications of anorexia and bulimia (see also supplemental handout)

- Avoid rapid refeeding if possible (nasogastric/NG feeding or total parenteral nutrition/TPN) → can cause severe anasarca (widespread edema) and cardiac failure.
- Dehydration → contraction alkalosis (increase in blood pH due to loss of fluid volume) in bulimia
- hypokalemia
- hypomagnesemia
- cardiac arrhythmias
- renal complications
- tetany
- grand mal seizures
- gastric rupture
- esophageal tears
- Osteoporosis/fractures
- vitamin deficiencies

8) Describe the psychological and pharmacologic treatment of eating disorder, broken down by the stages of treating disorders involving motivated behaviors:

a) Stage 1: Address the behavior

- Unlike treating a disease or engaging in traditional psychotherapy, goal is NOT to first understand the primary initiating factors and primarily address them (eg Penicillin for pneumococcal pneumonia)
- "The anorexic starves herself today in large part because she starved herself yesterday" → break the habit
- May require hospitalization to take control of the behavior or if medical complications severe enough
- A few powerful positive and negative contingencies (eg required bed rest until weight gain pattern apparent), along with early attempts at education
- Requires repeated vigilance through objective measures (the scale) and clear target weight (Metropolitan life tables, 10% of IBW) and "confrontation with concern"
- Minimize conflicts over the eating behavior itself by focusing not on this but on weight gain.

b) Stage 2: Address the medical complications of the behavior (in addition to textbook, see the handout)

- Avoid rapid refeeding if possible (NG feeding or TPN) to avoid severe anasarca and cardiac failure. May be lifesaving in severe cases, however.
- Correction of dehydration essential to correct contraction alkalosis in bulimia; Correction of hypokalemia, hypomagnesemia
- Treatment of cardiac arrythmias, renal complications, tetany, grand mal seizures, gastric rupture, esophageal tears, osteoporosis/fractures, vitamin deficiencies.
- Take all complaints seriously, even when previously evaluated.

c) Stage 3: Address comorbid psychiatric conditions

(including which antidepressants one should be wary of prescribing when at a stage of illness where starvation and/or active binging/purging remain a factor (i.e.,potential complications of TCAs, bupropion, MAOIs, benzodiazepines)). Also be aware of the risks of SSRIs in the starved state of anorexia (including hypoglycemia and significant hyponatremia). Also include describing how no medication has been found to be effective during the starved stage of anorexia nervosa (with the only effective "medication" at that point being food).

Describe how there are more potential pharmacologic options for addressing the urges to binge and purge in cases of bulimia where the patient is not underweight.

Anorexia:

- There **is no specific, effective pharmacologic treatment for anorexia**

- ANTIDEPRESSANTS
  - SSRIs
    - **Risks of SSRIs in the starved state of anorexia include hypoglycemia and significant hyponatremia**
    - FLUOXETINE (PROZAC) doesn't appear to be effective in treating either depression or weight loss in anorexic patients in the starved state. It may be useful **in higher doses to prevent relapse** among patients with anorexia who have achieved their goal weight. So, it may be of some **limited adjunctive usefulness,** particularly in **weight-restored patients who still have depression or OCD symptoms**, but its utility for weight restoration is limited.
  - TCAs
    - TCAs such as AMITRIPTYLINE (ELAVIL) have been used in the past, particularly given that they can be associated with weight gain, but given that there is a **significant risk of cardiac arrhythmia and anticholinergic effects in emaciated individuals,** they are hardly ever used nowadays
  - TYPICAL ANTIPSYCHOTICS (e.g., Thorazine)
    - were tried in the 1960's (given that weight gain is a side-effect). However, there was a risk of seizures and no clear benefit on thought process or course at follow-up was found. Other risks also are significant (parkinsonism, tardive dyskinesia) and so these older agents are hardly ever used.
  - ATYPICAL ANTIPSYCHOTICS such as OLANZAPINE (ZYPREXA)
    - have been studied in small samples and found to be **modestly useful** (in open-label studies) in decreasing anxiety, depression and obsessive thoughts about food as well as increasing the likelihood of weight gain. Potential side effects include headache, nausea, abdominal pain or bloating, diarrhea, ankle edema, and dizziness, and one also needs to watch out for increased lipids and/or glucose.

Bulimia:

- SSRIs

    - few anticholinergic effects and less sedating than TCAs
    - appear to **help decrease urges to binge and purge**
    - They are the most commonly used psychotropic agents in bulimia. HOWEVER, they **carry the risks of hypoglycemia,** and of **sudden hyponatremia (and MS changes) in patients who already are sodium-depleted**
- TCAs
    - DOXEPINE (SINEQUAN): Effective H2-blocker, and can be useful in patients with gastritis/esophagitis, but highly **anticholinergic and sedating**.
    - CLOMIPRAMINE (ANAFRANIL) may be helpful with obsessional patients, but same problems.
    - OTHER TRICYCLICS likely also effective, but **risk of cardiac effects in patients with nutritional deficiencies and electrolyte imbalances**
- MAOIs
    - are effective in bulimia, BUT patients with Bulimia are nonspecific in eating and therefore at **risk for hypertensive crises** if don't follow required dietary restrictions (**tyramine reaction)**
    - Patients also volume-depleted and trouble controlling body temperature and at risk for hyperpyrexia, hypotension and syncope.
- BUPROPION (WELLBUTRIN) has been found to be effective, but **contraindicated in active bulimia due to high risk of seizures** (massive electrolyte fluxes with binging/purging)
- BENZODIAZEPINES
    - In general, **don't prescribe BENZODIAZEPINES: high risk of addiction** in these patients, **high seizure potential** (noncompliance and electrolyte imbalances)
- Medicines are not a substitute for continuing to address the primary problem of the behavior; conversely, may be unable to address the behavior while patient is severely depressed or anxious
    - Failure to appreciate this has contributed to **high mortality in anorexia** (increases over time, to **20% if followed for more than 20 years**)
- As with other behavioral disorders, goals may be modest and relapse is common

*Because the bulimic is typically normal weight, medications can cause fewer side effects and are somewhat safer for use than in anorexics.

d) Stage 4: Address internal and external reinforcers

(including the role of medical and psychological therapies, monitoring, the potential need for multi-specialist care [primary care physician, individual psychotherapist, nutritionist, possibly a psychiatrist, and possibly other individuals such as a separate therapist doing family therapy]

- Role of antibulimic medications for internal reinforcers
- Education/Psychotherapy (when patient cognitively intact and able to meaningfully participate): Role of life-stressors, family dynamics, fears of adulthood, etc.
- Modalities of psychotherapy: Individual, group, family. Best current research has involved cognitive and cognitive-behavioral therapy.
- Need to continue with intensive monitoring, avoid premature discharge, and beware of "empty" insight.

e) Stage 5: Relapse prevention in the ambulatory setting

(including recognition of the high rates of relapse and the importance of being "relapse-ready.")

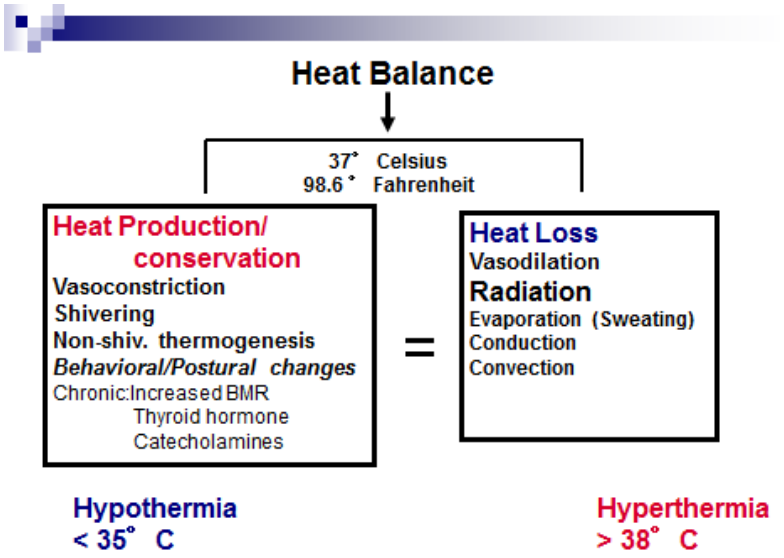
After discharge, focus shifts toward maintaining gains in natural settings. Patient and treatment-providers must be "relapse ready" with prompt return to program if this occurs

- Notoriously difficult:
  – New symptoms often arise with weight gain
  – Patients often unmotivated and resistant to forming treatment alliance with therapist
  – Limit setting must be combined with flexibility

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Regulation of body temperature
Karen Fairchild
Thursday May 5, 2011 10:10-11:00 am

Handout and ppt are posted to course website.

1. List the physiological mechanisms by which humans maintain heat balance and state which is most important. State the thresholds for hyperthermia and hypothermia.



2. Describe the physiological mechanisms by which heat loss is regulated by sweating, vasodilation/vasoconstriction and shivering. Describe the roles of the adrenal and thyroid glands in thermoregulation. Describe the role of brown fat in thermoregulation.

- Sweating
  - Most sweating is via eccrine glands (vs. apocrine)

Regulated by anterior & preoptic hypothalamus
-Behavioral/postural changes are the most important mechanism (one of the reasons babies cannot thermoregulate efficiently is that they are unable to properly modify behavior/posture)

-
  - autonomic, cholinergic pathways catecholamines (epi, norepi)
- Baseline low sweat rate, little NaCl in sweat (Most NaCl is absorbed in duct)
- Maximum sweat rate (1 liter/hr): high NaCl (1⁄2 normal saline)
- "Acclimatization" to hot climate (in 2-6 wks): increased sweating (2-3 L/hr), less NaCl loss in sweat via aldosterone
- **Allows evaporative heat loss (water travels to skin surface and evaporates taking large quantities of heat with it, this is impaired by high humidity)**

- Vasodilation/Vasoconstriction
  - **The subcutaneous venous plexus can accommodate from receiving 0% (need to conserve heat) to 30% (need to dissipate heat) of the cardiac output**
  - Regulated by hypothalamus

- Shivering
  - Regulated by posterior hypothalamus
  - Afferents: Stimulated by peripheral thermoreceptors (cold sensors), inhibited by anterior hypothalamus (heat sensors)
  - Efferents: lateral columns spinal cord to anterior motor neurons

- **Muscle tone rises, feedback oscillation of muscle spindle stretch reflex**
- **Heat production rises 4-5x**

- Thyroid Glands
  - Body cooling stimulates the sympathetic nervous system, sending signals to the anterior hypothalamus which causes release of thyrotropin-releasing hormone (TRH)
  - TRH stimulates the pituitary to release thyroid-stimulating hormone (TSH) which stimulates the thyroid to produce T4, T3.
  - **Thyroxine (T4) increases the basal metabolic rate (BMR), generating heat and raising the core temperature**
  - Important for chronic (NOT acute) thermoregulation
  - Birth is a major cold stress to baby; BIG surge of TSH in first minutes of life
  - Hypothyroidism → cold intolerance
  - Hyperthyroidism → heat intolerance
- Adrenal Glands
  - Peripheral and central receptors sense temperature drop
  - Anterior/preoptic HT signals adrenal medulla to produce
    - Epinephrine
    - Norepinephrine
  - Catecholamines increase BMR, this generates heat to raise core temperature
- Brown Fat
  - Small adult mammals and hibernating animals have a lot of brown fat
  - In humans, only newborns have significant amounts
  - Location: neck, axillae, between scapulae, around aorta
  - Many mitochondria and capillaries make it appear brown
  - Activated by sympathetic nervous system (catecholamines) and thyroid hormone
  - **Protein thermogenin uncouples oxidative phosphorylation to generate heat rather than ATP**
  - May play a role in protecting against obesity and diabetes
  - Babies can increase BMR 100% with brown fat

3. Distinguish among the abnormal temperature states of fever, hypothermia and hyperthermia.

- Fever = Raised setting of the hypothalamic thermostat (set-point is raised)
  - Mechanism:
    - Pathogen-associated molecular patterns (PAMPs) bind to pattern recognition receptors (PRRs) on WBCs
    - Activated WBCs release pyrogenic cytokines (**IL-1beta**, TNF-alpha, IL-6)
    - Pyrogenic cytokines or microbial toxins stimulate COX2 in BBB to produce PGE2 in brain
    - PGE2 stimulates increased firing of neurons in pre-optic & anterior hypothalamus, thus increasing the temperature set-point
  -
- Hyperthermia = inability to dissipate excess heat (set-point is unchanged)
  - Review: Lesion to the anterior hypothalamus (responsible for heat reduction)
- Hypothermia = inability to generate sufficient heat (set-point is unchanged); endogenous, accidental, or induced hypothermia
  - Review: Lesion to the **P**osterior hypothalamus (responsible for heat **P**roduction)

4. Explain the conditions under which fever may be beneficial or detrimental. Explain the conditions under which hypothermia may be beneficial or detrimental.

- Fever
  - Benefits = **augmenting host defense mechanisms** (studies show increased chemotaxis, phagocytosis, pathogen clearance at febrile-range temperatures; increased survival in response to peritonitis, sepsis, viral infections)
  - Detriments = **collateral tissue injury** (studies show increased tissue damage with fever, e.g. increased lung injury in fever+pneumonia or fever+hyperoxia); **dangerous to the injured brain** (must keep body temp in low-normal range in patients recovering from stroke, head trauma, post-neurosurgery)
    - Fever increases metabolic rate and O2 consumption/demand; inability to keep up with O2 demand leads to tissue necrosis
- Hypothermia
  - Benefits = in adults following cardiac arrest and in full-term neonates with hypoxic-ischemic encephalopathy, induced

hypothermia was shown to decrease mortality and severe **neurological** morbidity; induced hypothermia may also have many other potential clinical applications and benefits (see handout, bottom of pg. 8)
    - cytoprotective/neuroprotective in ischemia-reperfusion and possibly in acute inflammatory processes
- Detriments = causes somnolence, confusion, slurred speech, decreased hand coordination, inhibition of shivering, pallor (adults), flushing (children), and 600 deaths per year
    - thermoregulation impaired when body temp < 35 deg C and is lost at < 30 deg C
    - bradycardia at temp < 34 deg C, V fib or asystole at temp < 28 deg C
    - associated w/ poor prognosis in sepsis, trauma, surgery, premature neonates

Mind, Brain and Behavior
Week 39: Higher Cortical Function
Neuro Case Discussion
Bart Nathan, MD
Thursday May 5th, 2011
11:10am-noon

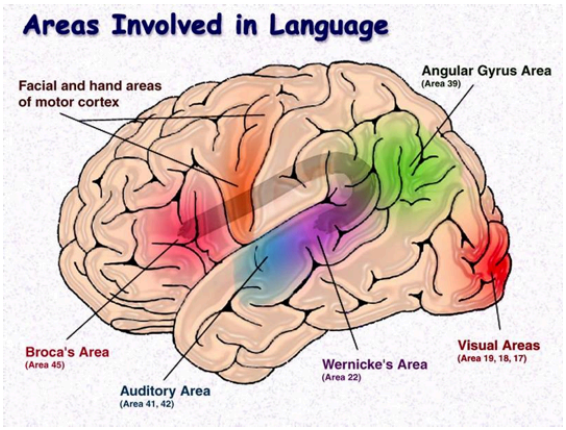
Review Objectives

1. Language

a. Define aphasia, prosody, automatic language, motor aphasia, sensory aphasia, non-fluent aphasia, fluent aphasia.

- Aphasia: Acquired disorder of symbolic language **processing**
    - Subtypes classified by relative impairments of different language domains
    - Separate from disorders of articulation (dysarthria)
    - Most are actually "dysphasia"- language is not completely absent
- Prosody: Rhythm, stress, and intonation of speech (Wikipedia)
- Automatic Language: reflexive in nature, like you stub your toe and say "crap" or "ow" without thinking about it
- Motor Aphasia: broken or slowed speech; may retain contextually sensical words throughout; they will write the way they talk
    - also called Broca's Aphasia (see below), expressive or non-fluent aphasia
- Sensory Aphasia: Wernicke's Aphasia, also called fluent aphasia and receptive aphasia (see below)
    - Speech is fluent (normal pace) but meaningless; impaired ability to comprehend spoken or written words

b. Identify Broca's and Wenicke's areas of the brain. Predict the consequences of a lesion in Broca's area and in Wernicke's area.



- Lesion to Broca's Area → Broca's Aphasia
    - can't write well either because they almost always have a hemiparesis
- Lesion to Wernicke's Area → Wernicke's Aphasia

c. Distinguish between the characteristics of Broca's aphasia and Wernicke's aphasia in terms of the following: characteristics of spontaneous speech, facility for naming, auditory comprehension and repetition.

	Broca's Aphasia	Wernicke's Aphasia
Characteristics of Spontaneous Speech	Non-fluent, hesitant, from mute to agrammatic, often dysarthric	Fluent with paraphasic errors of both phonemic and semantic type
Facility for Naming	Impaired ("tip of tongue")	Impaired, often paraphasic (substituting words for others inappropriately)
Auditory Comprehension	Intact for simple material	Impaired, often for even simple

	Impaired for complex syntactic constructions	questions
Repetition	Impaired, hesitant	Impaired

2. Cortical Organization and Deficits

a. Define the following clinical terms that describe dysfunction of association cortex: abulia, agnosia, prosopagnosia, apraxia, aphasia, agraphia, akinesia, perseveration, contralateral neglect. Recognize these features in a patient.

Terms that refer to disorders of cortical processing:

- Abulia = "non-will" ("*boule*" = "will" in greek)
    - loss of will or motivation
- Agnosia: inability to recognize categories of objects or faces, inability to identify objects using the senses
    - Visual agnosia, Auditory agnosia, etc
    - Anosoagnosia = "no knowledge of disease" [Greek *"nosos"* (disease) + *"gnosis"* (knowledge)]
        - a condition in which a person who suffers disability seems unaware of the existence of his or her disability
- Prosopagnosia = "ignorance of near face" [greek "*pros*-" (near) + "*opon*" (face) + "*agnosia*" (ignorance)]
    - inability to recognize specific faces
- Apraxia: loss of ability to execute learned motor movement
    - (higher-order movement motor ability remain intact
    - test movement, like "move your hand as though you're striking a match")
    - these patients can still read, so get them to read something like "close your eyes"
- Aphasia = "without utterance"
    - inability to comprehend and/or produce language
    - Broca's aphasia v. Wernicke's aphasia
- Agraphia = "without writing"
    - inability to write, regardless of the ability to read
- Akinesia = "without kinesis" = "without movement"
    - loss of spontaneous activity (sometimes characterized as staring into space)
- Perseveration: a behavior in which the patient constantly repeats the same action, whether or not it is appropriate
- Contralateral neglect = a type of hemispatial neglect
    - due to infarcts or acute lesions of parietal or frontal lobes, on one side
    - an inability to attend to objects, or even one's own body, in one side of their visual field, despite the fact that visual acuity, somatic sensation a ????
    - Usually on left-side as it's due to a lesion in the non-dominant hemisphere (for ~95% of people, the right hemisphere); they are frequently not aware that something is wrong, or that the left side of their bodies (it's most often left-sided neglect) belongs to them

Mind, Brain and Behavior
Week 39: Higher Cortical Function
TBL: Brain death and disorders of consciousness
Donna Chen MD, Lois Shephard JD, Mary Kate Worden, PhD and Bart Nathan, MD
Friday May 6, 2011 8:30-11:30 am

Before class:
Review learning objectives from class session "Coma and Brain Death" on Thursday May 5.
Required reading is posted to course website as a single pdf file.
1. UVA Health Sciences Medical Center Policy No. 0115
2. Berant, James (2008) Ethical Issues in Neurology (3rd ed). Chapter 11 Brain Death. pp 266-270. Wolters Kluwer, Lippincott, Williams and Wilkins.
3. Fins, Joseph. (2005) Rethinking disorders of consciousness: new research and its implications. Hastings Center Report.
4. Sokol, Daniel (2009) The slipperimess of futility. BMJ 338:1418.
5. Meisel et al, (2000) Seven Legal Barriers to End-Of-Life Care. JAMA: 284(19): 2495-2501.
6. Manno et al. (2006). The declaration of death and the withdrawal of care in the neurologic patient. Neurol Clin 24: 159-164.

1. Define and differentiate among coma, brain death, vegetative state, minimally conscious state, and locked-in syndrome. Explain generally the ethical and legal implications of these different conditions with regard to treatment decisions, including decisions to withdraw or withhold life-sustaining treatment. [Bernat on brain death, Meisel on PVS, Fins on MCS and PVS).

- **Brain Death**
  - The concept of brain death is lawful in most jurisdictions, so there is no *legal* requirement not to declare brain death. However, unless the physician is confident that the family does not oppose this determination on religious grounds, the physician has an ethical obligation to delay. The physician has no ethical obligation to aggressively treat the brain dead patient. The physician may choose to continue aggressive treatment out of respect for the family's religious beliefs.
  - Refusal of families to accept brain death is more common from emotional or psychological difficulty rather than religious reasons. While there may not be a legal obligation for the physician to communicate with families regarding brain death and withdrawal of treatment, the ethical duty is to explain the concept, practice, and legality of brain death determination.

- **Locked in state** - patients with absent motor function, but intact sensory and cognitive function (resembles a coma, but patient retains ability to engage in vertical eye movements and blinking; no horizontal eye movement)
  - Usually due to infarct in ventral pons affecting bilateral corticospinal & corticobulbar tracts
  - Sensory pathways & brainstem reticular activating system are spared ⇒ patient is thus fully aware, able to hear, feel, understand
  - Vertical eye movements are spared b/c they are controlled by the riMLF (in the tegmentum of the rostral midbrain)
    - Horizontal eye movements are affected b/c they depend on pontine circuits

- **Coma** - unarousable unresponsiveness in which the patient lies with eyes closed
  - unlike w/ brain death, during coma many simple or even complex brainstem reflexes can occur (e.g. VOR, intermittent stereotyped spontaneous movements, reflexive withdrawal from noxious stimuli)
  - "unresponsiveness" refers to absence of psychologically meaningful or **purposeful** responses that are mediated by the cortex
  - EEG can show many different patterns, but is typically monotonous w/ little variability over time (unlike the normally varying EEG seen during sleep)
  - Cerebral metabolism reduced by at least 50%

- **Brain death** - irreversible lack of brain function (from a known cause); extreme form of coma in which clinical exam shows no evidence of forebrain or brainstem function (no brainstem reflexes), EEG shows brain inactivity, and cerebral metabolism and perfusion are reduced to 0

- **Vegetative state** - period following coma in which patient regains sleep-wake cycles, primitive orienting responses, and reflexes mediated by the brainstem and hypothalamus, but remains unconscious

- **Persistent vegatative state** - vegetative state described above lasting > 1 month
  - as in coma, no purposeful responses to stimuli, >50% reduction in cereberal metabolism indicating diffuse cortical dysfunction
  - unlike w/ coma, patients in PVS open their eyes and arouse in response to stimulation (via brainstem-mediated pathways)

- **Minimally conscious state** - can occur as further stage of recovery from vegetative state; minimal degree of responsiveness- can follow simple commands, say single words, or reach for /hold objects; no reliable interactive verbal or non-verbal communication & no reliable functional use of objects

2. Explain why physicians are legally allowed, but not legally required, to remove ventilator support in persons who are dead by neurological criteria. [Bernat]

Basically to allow room for "compassionate and diplomatic management" in cases where families reject the concept of brain death for one reason or another.

- The physician of a brain-dead patient who is faced with a family's religious opposition to brain death determination has a dilemma. Because brain death determination is lawful in most jurisdictions, the physician probably has no legal requirement not to declare brain death.
- However, should he choose to determine brain death, he has an ethical duty not to act on this determination when it is likely that the family's opposition is based on coherent, valid, and well-established **religious grounds**, and is not simply an emotional or psychological inability to accept a dire diagnosis and prognosis.
- Physicians probably should continue to ventilate such patients rather than extubating them despite the fact that they fulfill brain-death tests. But because such patients have a "zero prognosis" for recovery, physicians have no compelling ethical duty to treat them aggressively (don't have to give drugs, etc). Some would maintain ventilation, but reduce vasopressors and await the inevitable asystole in a few hours-days.
    - Other physicians would continue all aggressive treatment out of respect for the family's religious beliefs.

- But what if the family objects not for religious reasons, but due to confusion about the concept of brain death or a desperate hope for recovery?

- Some argue that physicians declaring brain death have no duty to seek permission from families or even to inform them of the plan to extubate after brain death determination. Two state courts maintained that physicians were permitted to ignore a family's desire to maintain their loved one on a ventilator once brain death was determined.
- Physicians' ethical responsibilities in this situation:
    - communicating effectively with the patient's family
    - explaining the concept and legality of brain death
    - explaining that the ventilator is the only thing keeping the patient alive and that there is no prospect for further recovery, that the diagnosis is certain, etc.
- Majority of families will accept the explanation and not oppose extubation. A minority will reject and demand continued treatment (either do not understand/accept the concept or think the doc is wrong).
- Physician has the choice here between extubating over the family's objections or continuing to ventilate. If you continue to ventilate, you don't have to continue other meds (e.g. vasopressors, mentioned above)-- may be easier for the fam to accept a CP death b/c it seems more natural.

- "Physicians have an ethical duty to help relieve a family's anxiety when possible, but this duty must be balanced carefully against their responsibility to conserve scarce medical resources and their duty not to prescribe futile therapies."

- Some insurance cos won't pay for hospitalization expenses after brain death is determined-- physicians have a duty to explain this possibility to the fam.

3. Describe religious differences in acceptance of death by neurological criteria, and how these differences are reflected in state law. [Bernat]

- Most religions accept the concept of brain death as consistent with their teachings. Religions for which there may be some inconsistency:
    - conservative Roman Catholics (but mostly accepted as fully consistent with teachings of RC)
    - Split among Orthodox Jews (no overarching authority to dictate opinion) - those who believe brain death is equivalent to decapitation and those who believe there is a difference between a sign of death (*i.e. cessation of respiration)* and death itself (*cessation of heartbeat)*--> but only a very small minority of strict Orthodox Jews embrace this latter position.
    - Generally accepted among Muslims
    - "There have not been specific pronouncements on brain death...from Confucianism and other Eastern religions."
    - Technological advances in Japanese medicine have led Japanese traditional Shinto and Buddhist societies to gradually accept the concept of brain death.
- All states permit some form of legal recognition of brain death. Since 1991, states have begun to include religious

exemptions. For example, the New Jersey statute states: “The death of an individual shall not be declared upon the basis of neurological criteria...when such a declaration would violate the religious beliefs or moral convictions of that individual and when that fact has been communicated to, or should ... reasonably be known by, the licensed physician authorized to declare death.” (family must demonstrate evidence of "reason to believe" this)

4. Describe UVA policy /Virginia law on brain death evaluation. [UVA policy]

- “**Death by neurologic criteria** shall mean the **irreversible cessation of all functions of the entire brain**, incl. the brain stem.”

A person is deemed medically and legally dead if:

1. absence of spontaneous respiratory and cardiac functions AND attempts at resuscitation would not be successful (“**cardiopulmonary death**,” can be diagnosed by any physician)
2. absence of brain stem reflexes and spontaneous brain and respiratory functions AND attempts at resuscitation would not restore (a.k.a. **brain death**; neurology, neurosurgery, electroencephalography, or critical care specialists/intensivists only)

II. Diagnosis of Death by Neurologic Criteria (additional details)

- Dx can only be applied to pts older than 7 days (assuming a normal term of 37 weeks post-conception, so technically 38 weeks into development)
- Dx must be made by a resident or attending in any of the aforementioned neuro specialties and confirmed by a second resident or attending of any specialty

A. Pre-reqs

1. **Demonstrate clinical or neuroimaging evidence** of a CNS injury sufficient to cause irreversible cessation of brain fx to establish cause of coma.
2. **Exclude possibility of recovery** of any brain fx by excluding complicating medical conditions, including: hypothermia, intoxication, sedatives/hypnotics, neuromuscular blockade, severe electrolyte abnormalities, severe acid-base anomalies, shock
3. If cause of coma cannot be established/clinical assessment confounded, infer irreversibility only after extended observations or confirmatory testing.

B. Clinical Exam: Cardinal findings = unresponsiveness, no brainstem reflexes, apnea

1. Unresponsiveness = No cerebral motor response to pain in all extremities, absence of seizures, shivering, or posturing. (Spontaneous body movements okay -> generated by spine).
2. Absence of brainstem reflexes = no response to bright light, no spontaneous eye movement (e.g. VOR test), no bulbar musculature (e.g. corneal, gag, sucking, rooting reflexes)
3. Apnea Test = can the pt. breathe unaided? (turn off the ventilator and observe CO_2 levels)
4. If any of the above three cannot be assessed, need confirmatory tests (see section C below).
5. Period of Observation - duration is a matter of clinical judgment
6. > 2 mos. old -> Period of **at least 6 hrs**. recommended when irreversible condition well-established, 24 hrs. for complex cases
7. < 2 mos. old -> Two positive (for brain death) **exams separated by 48 hrs.** recommended

C. Confirmatory Tests - required when cardinal findings from B cannot be reliably established

1. Cerebral angiography demonstrating absence of blood flow in intracranial arteries
2. Absence of intracerebral uptake of tracer isotope in nuclear imaging
3. Transcranial Doppler ultrasonography = Cannot be used to confirm brain death.
4. CTA, MRA, SPECT = Cannot be used to confirm brain death.
5. EEG and SEP = May be useful in confirming Dx of brain death but can only be reliably interpreted when all pre-reqs have been met

D. Implementation of Dx of Death by Neurologic Criteria (brain death)

- Communication and Documentation - Call the next-of-kin or surrogate! Document everything!
- “The Code of the Commonwealth of VA allows the physician to discontinue cardiopulmonary support at the time of death without consent from the next-of-kin or surrogate” (but physician’s choice of when to do so may be informed by other factors, such as...)
    - If the pt. is a suitable organ donor, can choose to continue CP support
    - Family Support: Ok to continue CP support if family cannot accept it; should not extend beyond 24 hrs.

5. Explain the "dead donor rule." [Bernat]

- Organs should only be taken from dead patients (can't pull from a vegetative patient, for example).
- The "dead donor rule" separates roles of determination of death and procurement of organs. To protect the donor from being incorrectly diagnosed as brain dead simply to permit organ procurement, the patient/organ donor must be dead and no member of the transplantation team may participate in the donor's brain death determination. This also improves the donation consent rate.

6. Explain how concerns over conflict of interest have led to restrictions on which physicians may participate in the determination of death of a potential organ donor. [Bernat]

- Brain-dead patients are the only proper donors for hearts and the main source for lungs, livers, pancreases, and kidneys.
    - To protect the donor from being incorrectly diagnosed as brain dead simply to permit organ procurement, it is axiomatic that the organ donor must be dead ("dead donor rule") and that no member of the transplantation team may participate in the donor's brain death determination.
- Strict separation is esp. important in organ donation after cardiac death due to the preceding decision to discontinue life-sustaining therapy.
- There is evidence that "uncoupling" the brain death determination from the organ procurement process in the family's mind also improves the donation consent rate.

7. Appreciate that family members may have difficulty understanding the concept of "brain death." [Bernat]

- Many family members do not realize that brain death means the patient is *legally* dead. The concept is counter-intuitive for some, especially when the brain dead patient still has other signs of life like a heartbeat, warm skin, and urine production. The media often misuses the term brain death, further confusing the public.

8. Appreciate that the misuse of terms like "vegetative," "brain dead," and "life support" can be confusing to families, yet frequently occurs in the media and in clinical care. [Fins, Bernat]

- The term "life-support" implies that the brain dead patient is still alive. It is important for physicians to explain that, in the absence of "life-support" such as a ventilator, the brain dead patient would have died immediately from cessation of respiration and heartbeat.
    - Try to avoid the terms "life-support" with respect to ventilation and "allowing them to die" with respect to extubation
        - stress that the patient is not simply in a coma but is biologically and legally dead and cannot recover
    - No patient fulfilling brain death tests has ever recovered, irrespective of treatment.

9. Appreciate that the existence of some consciousness in a patient with severe neurological deficits makes the ethical and legal questions relating to continuing or discontinuing medical treatment more challenging than when a patient is in an irreversible vegetative state (lacking any evidence of consciousness). [Fins]

10. Appreciate the different ways in which the term "futility" is used and misused. [Sokol]

- Futility is goal-specific and subjective.
- Physiological futility: When the proposed intervention **cannot physiologically achieve** the desired effect.
    - (e.g. prescribing antibiotics to treat a viral illness)
- Quantitative futility: When the proposed intervention is **highly unlikely** to achieve the desired effect.
    - Intervention may be withheld or withdrawn because it may be deemed wasteful or would deprive others of benefit
    - (e.g. a procedure that has only worked 1% of the time, or correctly guessing a card out of a deck)
- Qualitative futility: When the proposed intervention, if successful, will likely produce such a **poor outcome** that it is deemed **best not to attempt it**
    - (e.g. choosing not to attempt CPR on a badly mauled patient because even if successful, the patient's quality of life would be very low)
- The term futile should not be used in front of patients or family, as it suggests nothing can be done or attempted.

11. Explain why the concept of futility is most appropriately used to refer to "physiological futility." [Sokol]

- Physiological futility is the most objective form and is a binary concept - a given treatment can have a chance of working or can have no chance of being successful.

- Suggests that the intervention cannot improve the patient's physiological status (the only real desired outcome)

12. Describe the ethical and legal consensus concerning the relationship between withholding and withdrawing life-sustaining treatment (i.e., are they treated similarly or differently?) [Meisel]

- Although many clinicians think and feel differently about these types of actions, **the law and medical ethics treat the withholding and the cessation of life-sustaining treatment the same**. This includes the withdrawal of artificial fluids and nutrition; the treatment can be withheld or withdrawn if the patient refuses treatment or, if incapacitated, if there is consensus among the surrogate decision makers that the patient would choose to have the treatment withheld or withdrawn.
- Since the death of the patient results from the patient's underlying condition, there is no legal liability.

13. Know that numerous state courts have given their approval to the withholding or withdrawal of artificial nutrition and hydration to terminally ill and permanently unconscious patients if in accordance with patient preferences and appropriate surrogate decision-making. [Meisel]

14. Appreciate the importance of a physician's knowing the law of the state in which he or she practices regarding the requirements for withholding or withdrawing life-sustaining treatment, and appreciate that such laws may change. [Meisel]

- In New York, Missouri, Michigan, and Wisconsin, there must be evidence of an incapacitated patient's actual wish to forgo treatment under some circumstances, with further variation between hospitals.
    - Not necessarily the case in other states (surrogates, etc, may decide)
- Physician-assisted suicide is only legal in Oregon, Washington, and Montana but other states may still legalize or approve it (the Supreme Court ruled that laws making aiding suicide a crime do not violate the US Constitution, but not that states cannot legalize physician-aided suicide. Some states have made it legal; some have made it a crime)
    - Terminal sedation is legally acceptable (though untested in courts; see next LO for more)
    - It is not legally permissible in any state for a physician to administer a substance to a patient with the intent to end the patient's life, even at the patient's request or with the patient's consent. However, if the physician's intent is the relief of pain and suffering, and the patient dies as an unintended consequence, there should be no criminal liability under the principle of double effect (see next LO)
        - the Oregon law allows a physician to write a prescription for, but not to administer, a lethal substance

15. Define and describe the general ethical and legal understanding of the following: "euthanasia," "physician-assisted suicide," "doctrine of double effect," "terminal sedation," and withholding or withdrawing medical treatment. [Meisel]

- **Euthanasia**: the physician administers the lethal medication at the patient's request. Physicians openly practicing euthanasia are more likely to be vigorously and successfully prosecuted; it is not legal for a physician in any state to practice euthanasia, even if the patient is competent and requests it.
- **Physician-assisted suicide**: the physician provides the patient with a lethal dose of medication, which the patient must self-administer. The patient is (most likely) competent and terminally ill. This practice is only legal in Oregon (and Washington) and Montana, and physicians in other states who practice physician-assisted suicide could be subject to criminal prosecution.
    - everyone please note that the supplied article says "only... Oregon" (even though that may not be the case, it is important to recognize for assessment purposes) Drs. Chen and Shephard both know that it's also legal in these other states, and considering that, I don't think it's unreasonable to continue pointing it out. Besides, I really don't think there's going to be a question differentiating Oregon, Washington and Montana from other places. Since it is likely to come up in practice, it's good to point it out. Particularly since the article was written like 10 years ago.
- **Doctrine of double effect**: When an intervention is used for a legitimate purpose (e.g. pain relief) but has an unintended consequence that would be illegitimate if it were intended (e.g. patient death), the physician is not morally responsible for the unintended effect.
    - Supreme Court rulings and state laws recognizing a right to adequate palliative care confer varying legal protections on physicians to supplement the moral protection from the doctrine of double effect.
- **Terminal sedation:** An integration of two legally accepted clinical practices, (1) sedation of the patient to unconsciousness or a level that ensures escape from intolerable suffering, and (2) withholding life-sustaining therapy including food and fluids.
    - Terminal sedation is an alternative to physician-assisted suicide in states in which the practice is illegal, but the concept of terminal sedation has not been tested in court.

- **Withholding or withdrawing medical treatment**: This practice is both legally and ethically acceptable so long as the patient requests it, or the patient's surrogate relates that this was or would be the patient's wish. In some states, it is even permissible to terminate life support with the surrogate's permission if the patient's wishes are not known, if termination of treatment is in the patient's "best interests." Determination of patient's wishes is best done through an advance directive or living will.

One week ‘til Spring Break!!! (But lets celebrate Cinco De Mayo in the Meantime, Happy Corona-mistmas) - **Ohhhhh yeaaaaaaa!**

i just lold my pantalones off