Brain and Behavior Review Packet

Part I: Lectures 1-6

v.2002

Lecture 1: Limbic Anatomy and Function

- 3 tiers of brain function : *lower tier* = brainstem/cerebellum (autonomic function etc.)
  middle = thalamus/basal gang./limbic (rate of thought and movement, emotion, memory)
  upper = cortex (high level sensory/motor, complex thought, memory storage)

- "limbic" means "belt", coined by Broca

- limbic system includes the following structures: amygdala, entorhinal cortex (in the temporal lobe, includes hippocampus), septal nucleus, anterior cingulate gyrus, orbitofrontal cortex

- typical limbic functions include: memory, cognition, mood/anxiety, social behavior, impulses

Cognitive belt- key for memory etc. Memorize sequence!

hippocampus → fornix → mamillary bodies → anterior nuc. of thalamus →

→ anterior cingulate gyrus → cingulum bundle (cingulum) → hippocampus

- *hippocampus(hc)* (shaped like seahorse, located beneath parahippocampal gyrus)
  blood supply = 2/3 PCA 1/3 MCA
  input to hippocampus is via entorhinal cortex, subiculum
  output from hippocampus is via fornix (to mamillary bodies and septal nuclei)

  functions: short-term memory formation, spatial memory, orientation, attention, mood
  right hippocampus = spatial (London cabbies) left hippocampus = verbal

  uses *many* neurotransmitters: ACh (from forebrain inputs), DA (brainstem inputs), NE

  involved in partial complex seizures, herpes encephalitis, anoxic injury
  Alzheimer's disease: entorhinal cortex and septal nuclei (ACh) – see plaques/tangles

- *mamillary bodies* - posterior nuclei of hypothalamus- necrosis due to thiamine deficiency in alcoholics → Wernicke-Korsakoff syndrome = amnesia, confusion, confabulation

- *anterior nucleus of thalamus* – lesion here due to PCA small branch infarct can lead to amnesia

- *anterior cingulate gyrus* - involved in attention, drive, speech initiation
  minor lesion = apathy bilateral lesion = akinetic mutism (alert, can't act spontaneously)
  abulia = severe inertia
  note: ant. cingulate activity predicts response to antidepressants

- *cingulum bundle* – may be cut (cingulotomy) to treat refractory depression, pain, OCD

Emotional Division – includes amygdala, olfactory areas, orbitofrontal cortex

- *amygdala* - responsible for attaching emotional "color" to sensory info
  - 2 groups of nuclei: basolateral (receives visual/sensory info) & corticomedial
  - receives major input from olfactory areas- so smells are pretty emotionally-charged
  - closely associated with orbitofrontal cortex, nucleus accumbens

  - output to septal nucleus (ACh) via stria terminalis
  - output to hypothalamus/brainstem via ventral amygdalofugal pathway

  - key role in startle reflex, flight/fight, appetite, mood, aggression, social behavior

  seizure activity in amygdala may generate smells (burning rubber), autonomic changes, autonomic behaviors, deja vu, depersonalization, fear (these symptoms may also be seen in panic attacks, which are associated with the amygdala and locus ceruleus (norepinephrine))

  - damage amygdala – individual can't recognize fear in others
  - bilateral amygdalectomy → Kluver-Bucy syndrome – hypersexual, hyperoral, placid

  important for emotional memories (which really stick with you- especially if you've got post-traumatic stress disorder) - an exciting/stressful experience releases epinephrine, cortisol etc., which enhance amygdala function

Structures that you should be able to identify:
hippocampus, fornix, mamillary bodies, thalamus, cingulate gyrus, cingulum bundle
amygdala, stria terminalis, ventral amygdalofugal pathway, hypothalamus

Lecture 2: Frontal Lobe Function and Dysfunction

- Phineas Gage – a 4 foot rod shot through his frontal lobe → remained alive, lost morality

- humans have a lot more frontal cortex than many other species

Frontal zones:

Primary motor areas (Brodman 4) input from thalamus, S1; output via internal capsule
damage → initially flaccid contralateral hemiparesis, then spastic

Premotor areas (Brodman 6) input from thalamus, S1; output to M1 and others
damage → apraxia, difficulty doing fine motor tasks

Frontal eye fields (Brodman 8) does voluntary eye movement, active visual search
damage → can't *voluntarily* move eyes away from side of injury, poor visual search

Dorsolateral frontal cortex- executive functions, integration of sensory info, consideration of possible responses and selection of appropriate response, persistence and flexibility

damage → difficulty integrating sensory info, can't create many ideas (for instance, figure types), may get stuck on one idea (*perseveration*)

Orbital frontal cortex - receives limbic and *olfactory* input, sends output to autonomic and endocrine structures. Helps determine *socially appropriate behavior,* some memory

damage → disinhibition (runs with whatever thought/idea happens to enter their heads), socially inappropriate behavior, anosmia, confabulation

Cingulate/SMA - connects with cortical, limbic structures, responsible for drive/motivation, environmental exploration.

damage → apathy, akinetic mutism, weird attentional deficits, alien hand syndrome

small areas of damage to subcortical tracts can mimic larger cortical lesions

Fronto-subcortical circuits

5 frontal-subcortical circuits are known, 3 are key in behavior regulation
- dorsolateral circuit = working memory, executive function
- orbitofrontal circuit = impulse and mood regulation
- anterior cingulate circuit = drive and motivational states

prefrontal cortex – central to dorsolateral and orbitofrontal circuits (see above)
integrates sensory info and memory to decide on coordinated response
receives major innervation (dopamine, NE, 5-HT, ACh)
often damaged in closed head injury, aging, dementia
↓ dorsolateral prefrontal dopamine activity = associated w/schizophrenia

general pattern of these circuits (know this!):
frontal cortex → striatum → globus pall/ subst. nigra → thalamus → frontal cortex

Disease patterns
↑ activity of frontal-subcortical loops → OCD
caudate damage → apathy, depression
(caudate/putamen also involved in Huntington's, Tourrette's, Parkinson's)
general subcortical damage → cognitive slowing, poor memory retrieval, depression
(due to demyelination in multiple sclerosis, HIV, arterosclerosis)
hypoxic injury → damage to globus pallidus, hippocampus, cerebellar purkinje cells
nucleus accumbens (dopamine) – involved in substance abuse

Dementia types

Korsakoff's (alcoholics): intrusion, disinhibition, confabulation

Frontal type dementia (Pick's) : early behavior/personality changes, executive/inhibitory problems, no frank amnesia, anterior atrophy

Alzheimer's disease: personality OK, naming/construction problems, frank amnesia generalized and hippocampal atrophy

Lecture 3: Clinical Neurochemistry

Neurotransmitters (NTs)

fast NTs = work through ion-channel- include GABA, glutamate
slow NTs = work through G-protein coupled receptors (GPCRs) and 2nd messengers

Catecholamines- receptor type: G-protein coupled receptors

PH TH* DDC DβH PNMT
Phenylalanine → tyrosine → DOPA → Dopamine → NE → Epi

* tyrosine hydroxylase = rate-limiting

Catecholamine action terminated by reuptake or metabolism (MAO and COMT).
Dopamine metabolites = DOPAC and homovanillic acid (HVA)

NOTE: *decreased catecholamine and serotonin activity is associated with depression*.

Dopamine – functions in motor activity, cognition, abuse/reward pathways
- cell bodies in substantia nigra (output to caudate and putamen) - motor fcn
- also in ventral tegmental area (output to striatum, nuc. accumb., med. temp. lobe etc.)
- also- cortex, hypothalamus, olfactory, retina

receptors: D1= most common (in striatum, cortex, nucleus accumbens etc)
D2= in striatum primarily
D3, D4, D5 = mostly in cortical and limbic regions (target these with antipsychotics)
D1 and D5 receptors increase cAMP via adenylate cyclase, D2,3,4 receptors inhibit AC

Drugs
- L-dopa for Parkinson's disease (dopamine can't cross BBB)
- Reserpine- causes neurons to dump monoamines into synapse- quickly depleted.
  This can help fix dyskinesias but can cause depression and hypotension
- Deprenyl = MAO B inhibitor- prolongs dopamine activity
- Cocaine, Cogentin, Wellbutrin- block catecholamine reuptake,
- Cocaine and amphetamine cause DA release
- Haloperidol (typical antipsychotics) block D2 R – get motor side effects (tardive dyskinesia)
- Clozapine (atypical antipsychotic)- blocks D4R mostly, therefore fewer motor side effects
  major side effect = agranulocytosis - also autonomic problems- dry mouth, fatigue..)

Psychosis is (usually) *TOO MUCH* dopamine activity* (the mesolimbic pathway)
Parkinson's is *TOO LITTLE* dopamine activity (the nigrostriatal pathway)

* the caveat here is that *reduced* Dopamine activity in the *prefrontal cortex* is also associated with schizophrenia (which causes psychosis) - don't worry about this detail.

Norepinephrine – functions in depression, anxiety, arousal, attention, sleep
- cell bodies in locus ceruleus (pons/midbrain) – projects to limbic, cortical, cerebellar, spinal….
- terminated mostly by reuptake, also by COMT and MAO (VMA = key metabolite)

receptors: alpha-1 and beta- 1 = post synaptic ; alpha-2, beta-2 = presynaptic

drugs: some antihypertensives (phenoxybenzamine, phentolamine) – block alpha 1 R
clonidine = alpha-2 *agonist* – treats hypertension... why??
yohimbine – alpha-2 *antagonist* – increases sympa tone, arousal, panic
tricyclic antidepressants (nortriptyline, desipramine) – block NE and serotonin reuptake
can help in panic disorder and depression

Serotonin (a monamine, but *not* a catecholamine)– sleep, mood, pain, nausea, psychosis
- cell bodies in dorsal raphe nuclei = around aqueduct
(project to striatum, limbic, cortex, cerebellum)
- also in caudal raphe nuclei (project to spinal cord) – regulate pain transmission

tryptophan → (trypt. hyroxylase*) 5- hydroxytryptophan → (AA decarboxylase) serotonin (5-HT)
* rate-limiting

- serotonin action terminated mostly by MAO (to 5-HIAA), but also some reuptake

receptors: 5-HT_1 = alter AC activity (and cAMP)
5-HT_2 = phosphatidylinositol pathway (PIP2)

drugs: MAO inhibitors – prevent breakdown of serotonin (and NE and DA)
tricyclics (imipramine, amitryptaline) – block serotonin and NE reuptake
LSD and buspirone (anti-anxiety) = partial agonists
methylsergide (for migraines) = antagonist
fluoxetine (prozac) = a selective serotonin reuptake inhibitor (SSRI)

- "serotonin syndrome" (too much serotonin because of drug treatments!) - confused, agitated, fevers, diarrhea, tremor, hyperreflexia, ataxia etc etc…. adjust the meds and they'll get better!!

Acetylcholine (neither a monoamine nor a catecholamine!) - memory, movement, autonomic
- cell bodies in nucleus basalis of Meynert and septal nuclei → connected to hippocampus and amygdala- loss of ACh is associated with *memory problems* in Alzheimer's Disease!

acetyl-coA + choline → (ChAT (choline acetyltransferase)) ACh

- termination of ACh action via acetylcholinesterase (AChE) and reuptake

receptors: both types are in CNS: nicotinic AChR, muscarinic AChR (several subtypes)
drugs : botulinum toxin- inhibits neuronal release of ACh → paralysis
tacrine – AChE inhibitor - may help in Alzheimer's Disease
pyridostigmine – AChE inhibitor - helps myasthenia gravis (improves strength)
atropine and scopalomine – block mAChRs- atropine= sympa-like effects
scopalamine – may cause brief memory loss

GABA – the major inhibitory neurotransmitter in the brain
- cell bodies everywhere, especially: striatrum, thalamus, spinal cord, med. temporal lobe
- synthesized from glutamate by glutamic acid decarboxylase (GAD)
- see decreased GABA in striatum of Huntington's Disease patients

receptors: are chloride channels- GABA binding causes Cl^- influx (~hyperpolarization)

drugs: benzodiazepenes enhance GABA affinity/activity → depresses CNS
barbiturates and EtOH- also cause GABA chloride channel opening
bicuculline- GABA receptor antagonist → induces seizures… why?
picrotoxin inhibits Cl^- channel → induces seizures

Glutamate - a major excitatory neurotransmitter-
- glutamate blockers to help stroke recovery (because glutamate is involved in excitotoxicity)
- PCP and MK801 = glutamate antagonists that cause psychosis
- riluzole (for ALS/Lou Gehrig's dz) and lamotrigine (for epilepsy) decrease glutamate activity

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Nitric Oxide- functions in vasodilation (by stimulating guanylate cyclase to form cGMP),
Also functions in immunity, CNS/PNS etc.

- synthesized from arginine by nitric oxide synthase (NOS)
- Viagra – inhibits cGMP metabolism, therefore more cGMP = more blood flow

Lecture 4: Neuroimaging

CT scanning- Cheap, fast, uses X-rays

Good for diagnosing: acute bleed, stroke, brain atrophy (e.g. dementia), bony problems, hydrocephalus. Use iodinated contrast to look at tumors and inflammation

Bad for anything in the posterior fossa, bad for looking at white matter

Bright on CT: acute blood, contrast, bone, calcium, metal
Dark on CT: Air, CSF/water, old blood

Bone, brain, and water look different on CT because they have different densities. Things that stop the X-ray from passing through (e.g. bone) appear bright.

MR scanning- More expensive, slower, uses magnetic fields, better resolution than CT

Good for diagnosing: lesions causing epilepsy, anything involving white matter (axons), demyelination, posterior fossa lesions, frontal atrophy, herpes encephalitis

Bad for people with pacemakers or metal devices, claustrophobic patients

Different scan types: **T1** (tissue=grey, CSF= *dark*) **T2** (tissue=grey, CSF= *bright*)

Indications using for MR contrast are less clear than those for CT contrast, but, as a general rule, MR contrast (gadolinium) is most frequently used when infection or neoplasm are being considered.

Various tissues look different on MR because the protons in those tissues respond differently to the magnetic fields created by the MR scanner.

Safety Note: CT contrast is more toxic and can cause allergic reactions and renal failure. MR contrast (gadolinium) is generally safer. Also CT scans expose the patient to x-ray radiation, while MR scans expose patient to less-harmful magnetic field.

SPECT and PET- functional techniques to measure brain activity (cerebral blood flow etc.)
See areas of decreased CBF in dementia, or regional CBF increase during seizure

Using the neuroimaging program, learn to -
- identify scan type (CT, MR T1, MR T2, contrast/no contrast)
- describe lesions (small, medium, large, bright=high signal=hyperdense)

- identify key landmarks: all ventricles, calcifications (choroids plexus, pineal basal ganglia), internal capsule, basal ganglia, thalamus, hippocampus etc.

- identify key abnormalities: **stroke** (wedge shaped, dark on CT, know ACA/MCA/PCA) **acute bleed** (bright on CT), **multiple sclerosis** (bright periventricular white matter on MR), **herpes encephalitis** (bright medial temporal lobe on MR), **Alzheimer dz** (widespread cortical atrophy), **Pick's disease** (frontal cortical atrophy), probably a few others….

Lecture 5: Obsessive-Compulsive Disorder

note: most psychiatric diagnoses require that the disorder interferes with normal daily functioning

- OCD is characterized by intrusive obsessions (fear of getting dirty, infected, injured…concern with symmetry, organization) and compulsions (performed in response to obsessions, e.g. handwashing, checking etc.) (think *As Good as it Gets)*

- usually presents in early teens/20s - males have it earlier and worse
- genetic evidence – twin concordance, familial tendency
- OCD = assoc. with mood/anxiety disorders, repetitive behaviors (e.g. Tourette's)
  = assoc with ↓ serotonin (SRIs alleviate symptoms, antagonists provoke symptoms)

- circuit dysfunction: frontal cortex → striatum → globus pall. → thalamus → frontal cortex

- PET/fMRI show hyperperfusion in all above structures (*especially orbitofrontal cortex and anterior cingulate and especially on RIGHT side)

- primary dysfunction = basal ganglia? (screwed up/ hyperactive motor programs in OCD)
- possible treatments to slow down the circuit: SRIs, behavioral therapy,
  also: rTMS trials (noninvasive magnetic stim), neurosurgery = LAST RESORT
  (capsulotomy, ant. cingulotomy, limbic leukotomy)
- best current initial treatment = combination of drugs and behavioral therapy

- drugs (only work if they inhibit serotonin reuptake = SRI)
  clomipramine most effective - side effects = sedation, anticholinergic, ↓ sex drive, ↑ weight
  fluoxetine – side effects = as above, also anxiety and agitation initially
  fluvoxamine – similar to above- watch out for "rebound" symptoms if you quit drug quickly
  paroxetine and sertraline – characterized by sedation and "rebound" symptoms (as above)
  citaprolam – well-tolerated- side effects – nausea, anticholinergic effects

note: benzodiazepenes may help blunt initial anxiety probs
  trazodone, tricyclics, benzodiazepenes etc. may help with insomnia
  consider combination (e.g. clomipramine + another SRI) – data shows this works better

- behavioral therapy- expose patient to symptom-triggering situation, but don't allow them to perform compulsive or avoidance responses… slowly build up ability to handle triggers

Lecture 6: Neurobiology of Schizophrenia

Schizophrenia: a chronic and often progressive disorder of thought, affect, behavior, perception

- "positive symptoms" -actively doing something weird: hallucination, delusion, bizarre behavior
- "negative symptoms" – NOT doing something that normal people do: alogia (lack of speech), affective blunting, avolition, anhedonia, attentional impairment

Various Brain Regions in Schizophrenia

Cortex (6 layers): receives all major sensory info through thalamic relays,
other inputs come from all over (VTA- dopaminergic (DA) inputs, raphe – 5-HT inputs)

- association cortex – integrates sensory info, memories etc. → representation of experience
  layers 2, 4 have small interneurons (GABAergic, inhibitory)
  layers 3, 5 have big pyramidal cells (glutaminergic, excitatory)

- DA and 5-HT inputs (at receptors D1, D4, D5, 5-HT_{2A}) modulate sensory info processing
- schizophrenia – ↓ in cortical D1 receptors (seen on PET scan), and maybe ↓ 5-HT_{2A} receptors
- note: hallucinogens (LSD) = HT_{2A} agonist ; some atypical antipsychotic meds = HT_{2A} antag.

- neuroimaging shows ↓ volume of association cortex in schizophrenics, also regional cerebral blood flow (rCBF)and glucose metabolism are abnormal in frontal and temporal lobe structures (both at rest and during mental task performance)

Hippocampus
- long-term potentiation (LTP)= synaptic changes necessary for memory, glutamate is key
- medial temporal lobe attaches emotional "valence" to experience
- schizophrenics have 50% decrease in nonpyramidal cells here, also synapses/plasticity change also ↑ rCBF/metabolism in hippocamp at rest- further ↑ during positive symptom episodes

Thalamus- an information filter for the cortex
- in schizophrenia, perhaps the filter isn't working well, allowing to much sensory stimulation
- or maybe…. MD (mediodorsal) nucleus dysfunction alters function of cortical assoc. areas

Basal Ganglia = ventral striatum (nuc. accumb), dorsal striatum (caudate/putamen), glob. pall.
- dorsal striatum- responsible for regulating motor behavior - mostly D1 and D2 receptors
- ventral striatum = part of limbic system, nucleus accumbens is involved in reward/addiction
  mostly D3 receptor
- amphetamines and schizophrenia cause ↑ dopamine and mesolimbic hyperactivity
- schizophrenics- see ↑ striatal neurons and ↓ nucleus accumbens neurons

overall theory : ↑ mesolimbic DA activity responsible for positive symptoms
↓ mesocortical DA activity responsible for negative symptoms

Neurochemical Models of Schizophrenia

- *the dopamine model*: stimulant psychosis (i.e. several days of gulping amphetamines)– causes paranoia, hallucinations, agitation.

- *the glutamate model*: prolonged phencyclidine (PCP) abuse (NMDA receptor antagonist) – causes chronic psychotic illness (looks like schizophrenia) also ketamine (another NMDA antagonist) produces transient psychotic symptoms (including negative symptoms)

- both amphetamine and ketamine can trigger psychotic episodes in schizophrenics at much lower doses than those required to do the same in normal individuals

- note: chronic NMDA antagonist administration causes the same sort of regional ↑ & ↓ in dopamine that you see in schizophrenia. Is the root of this disease a lesion in hippocampal or frontal cortical glutaminergic circuits?

Pharmacological Treatments

- traditionally block D2 receptor (haloperidol and other typical neuroleptics) - motor side effects
- atypical neuroleptics block D4 receptor
  or block 5-HT_{2A} receptors (which enhances mesocortical DA activity)

note- negative symptoms are much harder to treat than positive symptoms