Biopsychology

Brain Disorders

Lecture 10

Monday, March 19, 2012
5 overlapping neural systems that are involved in behavior (or behavioral disorders)
**The dopamine (DA) pathways in the brain**

Dopamine is transmitted via three major pathways.

1.) **Substantia nigra** sends projections to the Basal Ganglion ([Neostriatum system](#)) processes sensory stimuli and movement for habits.

2.) The **ventral tegmentum** sends projections to the forebrain ([Mesolimbic system](#)) and is associated with cognitive reward and emotional behavior.

3.) **Tubero-infundibular system** (Do Not need to know for Exam)

Dopamine: Active in maintaining and **initiating normal motor behavior**. Strongly involved in **Reward of specific behaviors and forming habits**.
The serotonin (5HT) pathways in the brain

The principal neuronal cell bodies for serotonergic neurons are the rostral and caudal raphe nuclei.

1.) From the rostral raphe nuclei axons ascend to the **cerebral cortex, limbic regions** and specifically to the **basal ganglia**.

2.) Serotonergic nuclei in the brain stem. (DO NOT NEED TO KNOW for EXAM).

3.) Prefrontal cortex (PFC) control of the a particular portion of the Raphe is responsible for producing favorable response to stressors. [i.e. **PFC provides Control over stress via modulating the a part of the Raphe**, we will see how next week!]

Active in maintaining **waking states**. Abnormal **increases activity** are associated with OCD, tics and Schizophrenia. **Decreases are related to major depressive states.**
The noradrenaline (NE) pathways in the brain

Many regions of the brain are supplied by the noradrenergic systems.

1.) The principal center for noradrenergic neurons is the locus coeruleus.

2.) The ascending nerves of the locus coeruleus project to the frontal cortex, thalamus, hypothalamus and limbic system.

Active in maintaining emotional tone. Decrease in NE activity related to some depressive states and increase is related to mania and anxiety states.
GABA pathways in a normal brain

GABA is the main inhibitory neurotransmitter in the central nervous system (CNS).

1.) **GABAergic inhibition is seen at all levels of the CNS**, including the hypothalamus, hippocampus, cerebral cortex and cerebellar cortex.

2.) GABA interneurones are abundant in the brain, with 50% of the inhibitory synapses in the brain being GABA mediated (Not shown).

**Literally everywhere! Plays a role in Depression as we will see.**

---

The glutamate pathways in the ‘normal’ brain

Glutamatergic pathways are: the cortico-cortical pathways; the pathways between the **thalamus** and the **cortex**; and the extrapyramidal pathways (not listed today).

- Other glutamate projections exist between the cortex (e.g. **PFC to Raphe**)
  - Glutamate-containing neuronal terminals are **ubiquitous** in the central nervous system and their importance in mental activity and neurotransmission is considerable.
  - Also plays a role in depression as we will see!
The hypothalamic-pituitary-adrenal (HPA) axis

HPA axis is composed of the hypothalamus (PVN specifically), the pituitary and the adrenal glands. Upon stimulation of the PVN, CRH, ACTH and CORT (Cortisol; stress hormone) are secreted. One function of CORT is the negative feedback regulation of the stress-stimulated PVN and pituitary activity. CORT modulates other brain regions (e.g., PFC, hippocampus, and amygdala). The sympathetic–adrenal–medullary (SAM) system leads to the release of epinephrine from the adrenal medulla, which is Adrenalin for fight or flight.

Release of CORT (via Basal or Stress) into the systemic circulation has a number of effects. **Long-term** elevated CORT activity leads to **neuronal cell atrophy**, but **short-term** (acute/phasic release) stress-stimulated CORT is functionally adaptive (we will see next week). CORT secretion in the PNS increases blood pressure, blood sugar levels, and has an immunosuppressive action. Thus, general effects **promotes metabolism** of carbohydrates, proteins, and fats (Promotes energy for energy) for fight or flight, or for recovery.

Chronic CORT General **Weakens** the activity of the immune system. Also associated with diabetes, cardiovascular disease, autoimmune disorders, asthma, osteoporosis. Effects of CORT in the CNS Brain are quite complex, but range from adaptive to maladaptive, as we will see.
Anxiety is a generalized mood that can occur without an identifiable triggering stimulus. Types GAD, PA, PTSD, Phobias and OCD.

Acute Anxiety = Normal psychological (CNS) and physiological (PNS) response to a stressor = Adaptive

Typical panic responses in phobia

The autonomic nervous system (ANS) controls the body’s internal environment by sending impulses from the central nervous system to the peripheral organs. The ANS is subdivided into the sympathetic nervous system (red) and parasympathetic nervous systems (grey). The sympathetic nervous system, which starts in the hypothalamus, is most active in times of stress, and stimulation of the peripheral organs (blue) produces a panic response (yellow), which produces a general increase in organ activity.
GAD, show signs of constant worry, view life as generally stressful. During passive activity, patients with GAD exhibit increased metabolic rates (fMRI) in the occipital, temporal and frontal lobes, as well as cerebellum and thalamus.

During vigilance tasks, GAD patients show increased metabolic activity in the basal ganglia. These finding suggests what? **That these patents display hyperactive brain circuits in GAD.**

- GAD patients display **hyperactive neurotransmitter circuits** between the cortex, thalamus, amygdala and hypothalamus.

- **Hypofunction** of serotonergic neurones (dorsal raphe nucleus) and GABAergic neurons that are widely distributed in the brain may result in what? **a lack of inhibitory effect.**

- **Overactivity** of noradrenergic neurones (locus coeruleus) may produce excessive excitation in the brain areas implicated in GAD.
The areas of the brain affected in post-traumatic stress disorder (PTSD)

Sensory input (hyper-vigilant), memory formation and stress response mechanisms are affected. This includes hippocampus, amygdala and frontal cortex. While the heightened stress response is likely to involve the thalamus, hypothalamus and locus coeruleus.

Atrophy of the hippocampus (MRI) and whole brain atrophy is exhibited by people with PTSD.

Develops after exposure to any event(s) that results in psychological trauma (e.g. repeated trauma such as torture/abuse or after single incident exposures such as car crashes and natural disasters). Traumas experienced early in life can increase the risk for developing PTSD.

Diagnostic symptoms for PTSD include re-experiencing the original trauma(s) through flashbacks or nightmares, avoidance of stimuli associated with the trauma, and increased arousal such as difficulty falling or staying asleep, anger, and hyper-vigilance.

Two physiological stress response hormone systems are thought to underlie the characterization of PTSD. The HPA axis and the sympathetic–adrenal–medullary (SAM) system. PTSD is typically associated with abnormally low plasma cortisol levels. Patients display increased and prolonged CORT sensitivity (responsiveness), which results in an enhanced control of the HPA axis (negative feedback inhibition). Interestingly, PTSD is also associated with greater sympathetic nervous system arousal (SAM) as reflected by catecholamine levels (e.g. NE or E).

Treatment = Prazosin: NE receptor Antagonist, very cheap and effective But politics have kept this drug in the dark!
The areas of the brain affected in **panic disorder (PD)**

PD, sudden intense fearfulness provoked by anticipation of danger accompanied by increased ANS (SAM) activity.

Increased serotonin activity in the amygdala and frontal cortex induces symptoms of anxiety. Increased activity in the periaqueductal grey results in defensive behaviours and postural freezing. Increases noradrenaline release (locus coeruleus) mediating arousal, while the hypothalamus mediates the sympathetic nervous system (typical in all Anxiety behaviors).
Regions of the brain implicated in obsessive compulsive disorder (OCD)

OCD, characterized by recurring, persistent, intrusive thoughts (obsessive, e.g. Contamination). Compulsions, are repetitive rituals to relieve the obsessive thoughts. When ignored patients feel overwhelming guilt, shame and anxiety.

Abnormal metabolic activity in the orbitofrontal cortex, the anterior cingulate/caudal medial prefrontal cortex [basically the PFC].

OCD patients exhibit increased metabolic activity in the cortico-basal ganglia network during rest and activation (e.g. hyperactive neurotransmitter circuits between the cortex, basal ganglia and thalamus) [Basal ganglia is for forming and maintaining motor habits].

Hypofunction of serotonergic neurons (rostral raphe nucleus) result in a lack of inhibitory effect on the putative OCD pathway.

Overactivity of dopaminergic neurones (substantia nigra) may produce excessive excitation in the brain areas implicated in OCD likely produces reward burst for habit behaviors.
Surgical treatment of OCD: For severe cases of OCD.

Psychosurgery; consist of surgical interruption of Limbic lobe (2–3 cm of white matter) at the anterior cingulate cortex disrupts transmission from the frontal cortex and reduces the symptoms of OCD.

Psychogenetics of obsessive-compulsive disorder

There is evidence for a strong genetic component in OCD. Associations have been reported for the low enzyme activity of the COMT (catechol-O-methyltransferase) gene and MAO-A (monoamine oxidase A), two enzymes involved in the neuronal metabolism of catecholamine transmitters (5 HT, DA, NE and E).
Mechanism of action of the benzodiazepines

GABA is the major inhibitory neurotransmitter in the central nervous system.

Benzodiazepines (BDZs) bind to the gamma sub-unit of the GABA-A receptor. Their binding causes an allosteric (structural) modification of the receptor that results in an increase in GABA A receptor activity. BDZs do not substitute for GABA, which bind at the alpha sub-unit, but increase the frequency of channel opening events which leads to an increase in chloride ion conductance and inhibition of the action potential. Overall this leads to decrease in CNS activity.
Depression

The areas of the brain affected in depression

Depression manifests in many forms. Reactive depression, is a normal response to many different events in life (loss of loved one). Clinical depression, is so severe that people withdraw from life, characterized by feelings of pain and loneliness. This state although similar to depression that we all experience, differs in intensity and duration!

Many areas of the brain appear to be involved in depression including the frontal and temporal lobes and parts of the limbic system including the cingulate gyrus. However, it is not clear if the changes in these areas cause depression or if the disturbance occurs as a result of the etiology of psychiatric disorders.

Remember that both 5HT and NE pathway projections from the Brain stem innervate similar brain regions, thus 5HT and NE systems overlap (slide 3-4).

Epidemiology of MDD

- Lifetime prevalence = 10-25% F; 5-12% M
- Gender ratio 2:1 (F:M) beginning in adolescence
- Age of onset: Current peak onset age 15-29 yrs.
- MDD does not discriminate w/ regards to ethnicity, education, income, or marital status
The hypothalamic-pituitary-adrenal (HPA) axis in depression

In depression, the hypothalamic-pituitary-adrenal (HPA) axis is upregulated, also CORT control of the HPA axis (negative feedback) is impaired. Over all depressed patients display a higher magnitude of basal (diurnal) CORT secretion (i.e. This leads to an excess of cortisol release). The receptors that bind CORT are likely down-regulated leading to disturbances in NE and 5HT brain activity (note that CORT receptors are located all over the brain).

So how does this really impact Health (i.e. Depression)?
The Role of BDNF (Brain derived neurotropic factor)

BDNF (acts as a NT, thus binds to a receptor) is a vital neurotrophic factor in the brain. Loss of BDNF contributes to depression. Exposure to BDNF in the hippocampus can lead to increased strength in some synaptic connections. Constant high circulating levels of CORT (via stress) have been shown to lead to a down regulation of BDNF in the hippocampus. Also, unregulated stressors lead to chronic elevated CORT release, thus decreasing expression of BDNF. Since BDNF is required for making and maintaining synaptic connections, down-regulation via CORT (very high levels) leads to neuronal atrophy (Figure above). Interestingly, BDNF upregulation and neurogenesis is somewhat restored by several antidepressants, suggesting that antidepressants reverse the atrophy of neurons that occur during depression.

Note: BDNF (peptide = protein) is a NT’s, and therefore binds to a receptor called TrkB. How then does BDNF contribute to neuronal growth and synaptic plasticity?
Depression
MAO-Is

Normal

MAOI = Acute increase in Amines (DA, NE and 5HT)

SSRI block reuptake, thus increase 5HT and NE. However, Auto-receptors decrease NT release and synthesis, resulting in reduced NT activity.

With repeated treatment (weeks) and changing dose, auto-receptors down regulate. Leading to an increase in 5HT. Postsynaptic receptors can down regulate too, so dose is increased.

So what MAOIs and SSRIs increase 5HT and NE! What does this Do on a molecular-neuronal, systems and behavioral level?

Increase in 5ht and NE (via MAOIs or SSRIs) via chronic treatment produces an increase in signal transduction (second messengers and kinases [signaling proteins]). Which lead to increases in gene activity and production of new proteins i.e. BDNF (and what is BDNF for?)
Problem with SSRI’s and MAOIs is that treatment takes weeks to titrate the effective dose, and most of the time these drugs are ineffective for most depressed patients.
**Depression: Ketamine treatment**

**History:** Ketamine is best known because of its use as an anesthetic in children and animals and is a drug of abuse (Jack-Ass SteveO).

When treating patients suffering from complex regional pain syndrome (CRPS) with a low-dose (subanesthetic) ketamine infusion, it was observed that some patients made a significant recovery from associated depression. This recovery was not formally documented, as the primary concern was pain management. It was not possible to quantify to what degree depression recovery was secondary to the patient's recovery from CRPS. *(Attention to detail is the key!)*

Ten years ago, ketamine was preliminarily tested at the Connecticut Mental Health Center as an antidepressant in low doses (non-anesthetic). The subjects were patients who previously resisted all other forms of treatment, but over two thirds responded positively to ketamine. Remarkably ketamine antidepressant effects were rapid *(effects took place within two hours of treatment and lasted more than seven days)*.

Ketamine has proven to be a fast acting treatment for major depression, by facilitating production of necessary proteins to be created to form brain connections. In short Ketamine is able to rapidly activate a component of the neuron that's responsible for new protein synthesis and in particular synthesis of proteins that are important for new synapses (BDNF?). It is believed that formation of new synapses and the connections between neurons that's important for the rapid action of ketamine in treatment of depression.

**To date** the absence of a drug treatment that works in hours rather than days-weeks-months on people at risk of suicide has not existed. Traditional treatments take weeks to months to work. However, the key disadvantages of directly using ketamine as an antidepressant are its use as a street drug and its toxicity from repeated dosages.

Research Problems to be answered: First, is to map what makes ketamine so effective and then search for another drug or drug component that is fast effective but free of dangerous side effects. **Second,** is to investigate a way to potentially sustain the rapid actions of ketamine. *One of the other limitations of ketamine is that while it does produce a rapid response or effective anti-depressant effect that only last for seven to ten days*. What is asinine about this statement?
Ketamine: in 2010, Duman’s lab (in Yale) discovered a completely novel pathway in how ketamine works to treat depression

“The story is in the signal transduction pathway,” unlike traditional antidepressants, which are generally auto-receptor or re-uptake inhibitors of NE and 5-HT, ketamine is a NMDA receptor antagonist (NMDA is an inotropic receptor that binds Glutamate, when activated it allows CA++ to enter the neuron which produces signal-transduction events). We will talk in depth about NMDA during the last week of class.

Ketamine activates the mTor pathway. mTor is a ubiquitous protein kinase involved in protein synthesis and synaptic plasticity in a process called synaptogenesis. Synaptogenesis restores the synapse connections in the brain that may deteriorate under stress and depression. Confirm synapse formation (below) by using a “two-photon imaging” showing increased spine density with ketamine treatment. Also blocking mTor pathway (with rapamycin), blocks ketamine’s antidepressant effects.

So if Ketamine is antagonist of the NMDA glutamate receptor how does it activate mTOR and BDNF to lead to synaptic plasticity (Synaptogenesis), remember that by definition antagonist promote no functional action just block receptor function?
Depression: Ketamine treatment

**5HT/NE Model of depression**

1.) Increase in 5HT and NE (via MAOIs or SSRIs) via chronic treatment produces an increase in 2.) signal transduction (second messengers and kinases [signaling proteins]). Which lead to 3.) increases in gene activity and production of new proteins i.e. BDNF (and what is BDNF for?)

**Ketamine Model of depression**

Ketamine stimulates BDNF, mTOR and synaptogenesis via neurotransmitter and intracellular signaling mechanisms:

1.) Ketamine stimulates glutamate transmission via blocking NMDA receptors activity on GABA inhibitory interneurons.

This increases AMPA (2) (Also, glutamate receptor) receptor activity via increased Glutamate NT activity on (2) resulting in BDNF release (3) and stimulates mTOR (4.), which stimulates synaptic protein synthesis (5). This leads to insertion of increased synaptogenesis (5), which contributes to the rapid antidepressant effects of ketamine.
Schizophrenia

The areas of the brain affected in schizophrenia

A number of regions of the brain are affected in schizophrenia. Changes reported in the parahippocampul gyrus may arise from abnormal neuronal development during formation of the cortex. Additionally, changes have been implicated in the basal region of the temporal lobe, the cerebellum and the mesolimbic system and PFC.

Classification of Symptoms

Negative Symptoms
- Flat or inappropriate affect
- Alogia-poverty of speech
- Avolition-Lack of goal directed behavior

Positive Symptoms
- Delusions-thought content
- Hallucinations-perceptions
- Disorganized thinking- language and thought process
- Disorganized behavior- self-monitoring
- Catatonic behaviors- decreased response to environment

Neurostructural Abnormalities
Neurodevelopment Model: Normal state (A) the mesocortical pathway (DA neurons in the ventral tegmental area/mid-brain/brain stem) and prefrontal (PFC: executive control) neurons provide inhibitory feedback onto limbic (emotions) areas.

(B) An early abnormality in schizophrenia is reduced mesocortical function, causing hypofrontal cortex activity leading to loss of inhibition of limbic activity via PFC. This may explain positive symptoms!
The areas of the brain affected in Alzheimer’s disease (AD)
The hippocampus is the area of the brain most affected by Alzheimer’s disease. It is there that the characteristic lesions of Alzheimer’s disease — neurofibrillary tangles and neuritic plaques — can be found. Neuritic plaques also occur throughout the neocortex. Atrophy of the parietal and temporal lobes is observed, as seen in the Alzheimer’s diseased brain is associated with disorientation in space and loss of language and memory.

Mutations in the tau gene lead to the abnormal aggregation of tau protein and the onset/progression of frontotemporal dementia. This finding demonstrates a role for tau production dysregulation in neurodegenerative disease. Gene mutations in result in alternative tau gene sufficient to produce nerve cell and glial cell dysfunction, leading to tau filament formation and degeneration.