non-exhaustive lists of terms and concepts for the 4 lectures of midterm 2

**from neuromodulators and drugs of abuse** - metabotropic receptor, phosphorylation of voltage gated ion channels, ionotropic receptor, 7 features common to all neuromodulatory systems, norepinephrine (NE), serotonin/5-HT, histamine (HA), acetylcholine (ACh), dopamine (DA), locus coeruleus, basal forebrain, posterior hypothalamus, raphe nuclei, ventral tegmental area, substantia nigra, functional anatomy (primary motor cortex and pyriform cortex examples).

**from spatial cognition** – reentry, autoassociative, hippocampus, tri-synaptic pathway, dentate gyrus, CA3, CA1, entorhinal cortex, depth perception from retinal disparity versus parallax, reference frames, head direction cells, grid cells, place cells, population/ensemble firing rate vectors, area MT, area VIP

**from basal ganglia and cerebellum** – spiny GABAergic neurons, purkinje cells, granule cells, pontine nuclei, cerebellar nuclei (fastigial, dentate, interpositus), inferior olive – climbing fibers, caudate/putamen/striatum, globus pallidus external segment, globus pallidus internal segment, substantia nigra pars compacta, substantia nigra pars reticulata, subthalamic nucleus, direct pathway, indirect pathway, hyperdirect pathway, D1 versus D2 dopamine receptors and enhancement of signaling at dendritic spines, reward expectation error

**from sleep and its function** – homeostasis, factor S, local field potential, temporal coherence of synaptic activity, theta rhythm, cortical EEG, desynchronized fast, spindles, slow-waves, rapid eye movement sleep (REM), stages 1-4 non-rapid-eye-movement sleep (nREM or non-REM), sleep cycle, sleep ”intensity”, REM-on neurons, REM-off neurons, VLPO neurons, orexin neurons, narcolepsy, K+ leak conductance, functions for sleep – metabolism, learning, development
It's a rather interesting phenomenon. Every time I press this lever, that post-graduate student breathes a sigh of relief.

Professor Nitz – circa 1986
neurotransmitters: mediating information exchange between neurons through generation of synaptic potentials

three basic types of neurotransmitter:

1. ionotropic excitatory (glutamate, ACh) – cause EPSPs
2. ionotropic inhibitory (GABA, glycine) – cause IPSPs
3. metabotropic / neuromodulatory (norepinephrine or ‘NE’, serotonin or ‘5-HT’, dopamine or ‘DA’, histamine or ‘HA’, acetylcholine or ‘Ach’)

EPSP and IPSP
characteristics of brain neuromodulatory systems:

1. small groups of neurons (10’s of thousands) sharing the same neurotransmitter (i.e., neuromodulator)

2. projections, via unmyelinated fibers, to widespread regions of the brainstem and forebrain

3. neurotransmitter binding to receptors generates, through phosphorylation, long-lasting (100+ ms) changes in properties of voltage-gated ion channels

4. firing activity of neuromodulatory neurons is strongly impacted by sleep/wake state (exception for dopamine)

5. neuromodulatory neurons receive input from a number of different sources, but all receive input from prefrontal cortex

6. low firing rates (mean approx. 0-6 Hz)

7. influence the neuronal responses to ionotropic excitatory and inhibitory inputs as opposed to directly mediating excitatory or inhibitory responses (i.e., alter the ‘functional anatomy’ of the brain)
projection patterns of the five major neuromodulatory systems of the brain

- **norepinephrine (NE) system:** main nucleus is the ‘locus coeruleus’ in the pons

- **dopamine (DA) system:** ventral tegmental area and substantia nigra area (both in midbrain) – note more localized projections

- **serotonin (5-HT) system:** several ‘raphe’ nuclei distributed in brainstem

- **histamine (HA) system:** the ‘forgotten one’ – neurons localized to posterior hypothalamus

- **cholinergic (ACh) system:** pontine and basal forebrain groups
examples of metabotropic pathways by which neuromodulators affect target neurons: the cyclic-AMP and phospoinositide (IP3) pathways to activation of protein kinases that phosphorylate ion channels thereby changing membrane potential and/or membrane potential responses to activation of ionotropic receptors
properties of ion channels:

* ion selectivity – e.g., Na+, Ca++, K+, Cl-
* gating – e.g., by voltage, ligand
* kinetics – e.g., open-time
* state – e.g., activated, inactivated, deinactivated, persistent, phosphorylated
* distribution – e.g., in dendrites, at axon hillock
neuromodulation I: alteration of ion channel kinetics through changes in phosphorylation state

Desai and Walcott, 2006: ACh decrements the responses of Ca++-dependent K+ channels thereby enabling greater initial responses as well as persistent responses to current injection (note…current injection mimics excitatory ionotropic input)

ACh alters K+ outflow caused by Ca++ influx (as seen when excitatory ionotropic receptors are activated)
neuromodulation II: uneven distribution, across dendrites, of ion channel responses to neuromodulators leads to alteration of neuronal responses to intrinsic, but not extrinsic inputs in pyriform cortex (note...pyriform cortex has only 3 layers)

Hasselmo et al., 1997: both norepinephrine and acetylcholine depress synaptic responses to excitatory inputs in layer Ib (intrinsic connections) much more so than to excitatory inputs to layer Ia (extrinsic connections) – that is, each change the degree to which pyriform cortex listens to the outside world (extrinsic inputs) versus the inner world (cortex→cortex or ‘intrinsic’ inputs)

- layer Ia inputs to dendrites of layer II neurons arise from olfactory bulb
- layer Ib inputs to dendrites of layer II neurons arise from other regions of cortex

in this case, both acetylcholine (mimicked by carbachol) and norepinephrine have the same action on Ib inputs
the long reach of neuromodulatory systems

drugs of abuse associated with neuromodulatory systems:

- **ACh**: nicotine
- **5-HT**: LSD, *ecstasy*, ‘magic’ mushrooms
- **NE**: yohimbine
- **DA**: *heroin*, *amphetamines* (e.g., ‘ice’), *cocaine* (also ‘crack’)
- **HA**: ?

treatment drugs associated with neuromodulatory systems:

- **ACh**: donezepil (Alzheimer’s)
- **5-HT**: prozac (depression, obsessive-compulsive disorder, anxiety)
- **NE**: desipramine (depression)
- **DA**: thorazine (schizophrenia), L-DOPA (Parkinson’s disease), Ritalin (attention deficit disorder)
- **HA**: antihistamines (insomnia)

neurological disorders associated with neuromodulatory systems:

- **ACh**: Alzheimer’s
- **5-HT**: depression
- **DA**: schizophrenia, Parkinson’s disease
is the dopamine system responsible for all pleasures and addictions?

The interactive effects of cocaine and imipramine on self-stimulation train-duration thresholds

Robert A. Frank, Thomas Pommering and Douglas Nitz
Department of Psychology, University of Cincinnati, Cincinnati, OH, USA

mediation of drug reward through the brain’s reinforcement learning mechanism

1. rats learn what to do to obtain VTA stimulation very quickly

2. mechanisms of drug action on the dopaminergic projection to nucleus accumbens (NAc):
   - cocaine – blocks clearance of dopamine from synapse onto NAc neurons
   - heroin – inhibits GABA neurons that inhibit dopamine (DA release increases through ‘disinhibition’)
   - nicotine – directly excites dopamine neurons
   - amphetamines – increase dopamine release through action at the axon terminal

3. Parkinson’s disease patients (who have <10% the normal amount of DA neurons) are deficient at reinforcement learning. Treatment with L-DOPA alleviates this.
principles of the week: ‘frame of reference’ and ‘reentry’
the hippocampus proper = dentate gyrus (DG) + CA3 + CA1
intrahippocampal and extrahippocampal connections (with cortex) exhibit patterns of convergence, divergence, and reentry at multiple scales
depth perception from motion parallax

or

depth perception from texture gradient

or

depth perception from occlusion

or

depth perception from retinal disparity (stereopsis)

but which?
EGOCENTRIC FRAMES

senses

musculature

ALLOCENTRIC (WORLD-CENTERED)

route-centered

object-centered

MAPPING SPACE IN THE BRAIN – RULE 2: DEFINE THE FRAME OF REFERENCE

egocentric frames

retinal space

eye position

hand space

arbitrary frames
tracking directional heading in the allocentric (world-centered) frame of reference: ‘head direction’ cells
– firing is tuned to the orientation of the animal’s head relative to the boundaries of the environment
– different neurons have different preferred directions (all directions are represented)
tracking directional heading: the ‘head direction’ cell

- firing is tuned to the orientation of the animal’s head relative to the boundaries of the environment (i.e., not to magnetic north)
- directional tuning may differ completely across two different environments provided that they are perceived as different

“N – heading” (relative to tracking camera)

90-degree rotation of the environment boundary dominated by a single cue card

distance along axis = firing rate of a single head direction neuron

Knierim et al., 1995
mapping position in the environment by path integration: ‘grid cells’

– neurons of the medial entorhinal cortex exhibit multiple firing fields in any given environment

– such fields are arranged according to the nodes of a set of ‘tesselated’ triangles

– grids, like head-direction tuning and place cells firing fields rotate with the boundaries of the environment

Hafting et al., Nature, 2005
medial entorhinal cortex contains grid cells, grid X head-direction cells, and head-direction cells – each cell type is also velocity sensitive, thus allowing for determination of position according to path integration (i.e., tracking of direction and speed over time) all within one structure.
tracking position in the world-centered (allocentric) frame of reference: the ‘place cell’
– firing is tuned to the position of the animal in the environment (the place ‘field’)
– different neurons map different positions (all directions are represented)
– rotation of the environment boundaries = rotation of the place fields
given that different hippocampal neurons bear different place fields, the firing rates of those neurons at any given time can be used to predict the animal's position in the environment.

For a set of neurons, the firing rates across the full set describe the ‘pattern’ of activity across the full population – this is called a ‘population firing rate vector’.

All brain regions appear to register information according to such ‘population’ patterns.
‘what’ (temporal) and ‘where’ (parietal) pathways in monkey and human

-damage to IT (TE + TEO) impairs object identification (but only via visual information)

-damage to parietal cortex (MT, MST, 7a, VIP, LIP) impairs visuospatial abilities (e.g., reaching to an object)

V4 = first site for figure/ground separation

MT / MST = detection of movement direction
along the ‘where’ pathway: area MST integrates optic and vestibular ‘flow’
area VIP of parietal cortex: bringing together personal spaces of the somatosensory and visual systems
mapping position in the egocentric frame of reference: area LIP maps position, relative to the space of the retina, for visual stimuli, the memory of them, and saccade direction

Barash et al., JNP, 1991
parietal cortex neurons in behaving rats map path segments (e.g., start pt. to first R turn)
parietal cortex: a rather abstract frame of reference – the space defined by the route (i.e., the space defined by sequence of behavior changes and the spaces separating them)

Nitz, Neuron, 2006
more parietal abstraction – ‘object space’ as a frame of reference for monkey parietal area 7a neurons

Crowe et al., JNS, 2008
together the triangles form an object the ‘top’ of which is perceived as indicated by the arrows – humans with damage to the right parietal cortex (and associated hemineglect) often fail to detect the gap in the triangle (red arrows) when it is on the perceived left side of the object (SE-NW) as opposed to the right (SW-NE)
BOLD SIGNALS IMPLICATE HIPPOCAMPUS AND PARIETAL CORTEX IN NOVEL SCENE CONSTRUCTION

Hassabis et al., JNS, 2007
basal ganglia and cerebellum

principles of the week: ‘reentry’ and ‘frames of reference’

the brain is not a strictly feed-forward system
– rather, the connectivity of most brain regions is characterized by a combination of feed-forward and feed-back (or ‘re-entrant’) inputs
the basal ganglia, hippocampus, and cerebellum – shared properties

1. each system receives input from widespread regions of cortex

2. each system outputs back to cortex (as well as to other regions)

3. each system is composed of several sub-regions across which information input from cortex converges and output to cortex diverges

4. each system is implicated in learning and each exhibits a unique form of learning at the cellular level

5. neurons within each system exhibit firing patterns related to ‘contextual’ information (i.e., activity not related to a single sensory or motor variable)
the cortex-cerebellum-cortex loop: role in timing and adjustment of motor patterns

- inhibitory projection
- excitatory projection

- cerebral cortex
- pontine nuclei (mossy fibers)
- convergence
- divergence
- convergence = coordination across muscles of the body

- cerebellum – granule cells
- vestibular and proprioceptive inputs
- inferior olive (climbing fibers - ‘error’ signal induces learning)

- cerebellum – Purkinje cells

- cerebellar nuclei (base of cerebellum – each contains homunculus)

- ventrolateral thalamus (and brainstem and spinal cord)

- motor/prefrontal cortex

- convergence

- divergence

- folia
- deep white matter

- parallel fiber
- magnified granule cell
- granule cell layer
- molecular layer
- white matter
- mossy fibers
- climbing fiber

- from the front...
- ...from the side
cerebellar function: the view from the cerebellar nuclei

......cerebellum – Purkinje cells

**cerebellar nuclei** (high baseline rates modulated by Purkinje cell inhibition)......

<table>
<thead>
<tr>
<th>fastigial nucleus</th>
<th>interpositus nucleus</th>
<th>dentate nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td>neuronal activity</td>
<td>eye mvmts. / walking</td>
<td>perturbation of limb/body from holding position</td>
</tr>
<tr>
<td>localized inactivation</td>
<td>posture and gait instability</td>
<td>tremor</td>
</tr>
<tr>
<td>function</td>
<td>postural adjustments</td>
<td>balance of agonist / antagonist muscles</td>
</tr>
</tbody>
</table>
basal ganglia: a complex of sub-regions damage to one or more of which is implicated in Parkinson’s disease, Huntington’s chorea, obsessive-compulsive disorder, Tourette’s syndrome, attention deficit disorder, and drug addiction.

together the caudate and putamen are called the ‘striatum’

substantia nigra has two sub-regions:
pars compacta = DA neurons
pars reticulata = GABA neurons (analogous to G Pi)

globus pallidus has two sub-regions:
external segment = GPe
internal segment = G Pi

the thalamic sub-region associated with the basal ganglia output is the ‘ventrolateral’ thalamus
convergence: all regions of cortex contribute

2/3’s of output to, prefrontal, premotor or motor cortex

Direct, indirect, and hyperdirect pathways

Cortex → basal ganglia → cortex
the direct and indirect pathways are modulated differentially by DA

DA neuron activity is, at least in part, driven by positive errors in reward expectation (i.e., getting more value than expected given a specific condition)
convergence: all regions of cortex contribute 2/3’s of output to, prefrontal, premotor or motor cortex

cortex → basal ganglia → cortex: direct, indirect, and hyperdirect pathways

- Direct path
- Indirect path
- Hyperdirect pathway

- GABA, enkephalin, D2
- GABA, substance P, D1

Excitation, Inhibition, Dopamine modulation
entire neocortex: combined motor and sensory context

'motor' neocortex: implementation of decision

'strong inhibition' pathway—favored by high DA levels

'strong excitation' pathway—favored by low DA levels

direct pathway

indirect pathway

strong inhibition

weak inhibition

strong excitation

weak excitation

striatum

GP external

GP internal

thalamus
homeostasis: the tendency of a system, esp. the physiological system of higher animals, to maintain internal stability, owing to the coordinated response of its parts to any situation or stimulus tending to disturb its normal condition or function.
the local field potential (LFP):
a measurement, like the membrane potential, of charge differences (voltages) between two regions of the brain – maximal fluctuations in voltage are produced by common fluctuations in membrane potential among a population of neurons.

LFP waves, like sound waves can be analyzed for power (amplitude) at different frequencies.
In mammals, sleep is broken down into two types: rapid-eye-movement or ‘REM’ sleep and non-rapid-eye-movement or ‘NREM’ sleep.

NREM sleep is further broken down into 4 stages corresponding to sleep depth (defined by no. of slow-waves and associated difficulty to arouse with sound or touch)

REM sleep, overall, is as similar to the waking state as it is to NREM sleep

Both REM and NREM sleep are actively induced by specific brain mechanisms

In mammals, sleep and wake states are most often defined by characteristic EEG / LFP patterns and their association with:

- presence or absence of eye movements
- degree of muscle tone
- pattern of breathing and heart rate
- type of mentation
the smaller the brain, the quicker the cycle - NREM-REM cycles recur about every 90 minutes in humans, about every 30 minutes in cats and about every 12 minutes in rats.

Slow-wave activity (as in stage 3-4 NREM sleep) decreases over the course of the night while REM sleep bouts get longer and longer prior to final awakening.
sleep, like temperature and food intake, is homeostatically regulated – following deprivation, more sleep and higher sleep intensity are observed……

but what, more specifically, is regulated?

1) a circadian component (C above)
2) an ‘S’ component which reflects the homeostatic component of sleep propensity
### Sleep Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Waking</th>
<th>NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical EEG/LFP</td>
<td>fast/low-amp/irregular</td>
<td>slow-waves/spindles</td>
<td>fast/low-amp/irregular</td>
</tr>
<tr>
<td>Trunk muscle tone</td>
<td>high</td>
<td>minimal</td>
<td>absent (paralysis)</td>
</tr>
<tr>
<td>Eye movements</td>
<td>frequent</td>
<td>none</td>
<td>frequent</td>
</tr>
<tr>
<td>Heart rate</td>
<td>high/variable</td>
<td>low/regular</td>
<td>high/variable</td>
</tr>
<tr>
<td>Breathing rate</td>
<td>high/variable</td>
<td>low/regular</td>
<td>high/variable</td>
</tr>
<tr>
<td>Mentation</td>
<td>vivid</td>
<td>minimal / transient</td>
<td>vivid</td>
</tr>
<tr>
<td>Hippocampal LFP</td>
<td>theta rhythm</td>
<td>slow-waves</td>
<td>theta rhythm</td>
</tr>
<tr>
<td>Cortex/thalamus</td>
<td>fast/irregular</td>
<td>slower/burst-pause</td>
<td>fast/irregular</td>
</tr>
<tr>
<td>ACh Neurons</td>
<td>high rate</td>
<td>lowest rate</td>
<td>highest rate</td>
</tr>
<tr>
<td>NE Neurons</td>
<td>high rate</td>
<td>very low rate</td>
<td>inactive (REM-off)</td>
</tr>
<tr>
<td>5-HT Neurons</td>
<td>high rate</td>
<td>low rate</td>
<td>inactive (REM-off)</td>
</tr>
<tr>
<td>HA Neurons</td>
<td>high rate</td>
<td>very low rate</td>
<td>inactive (REM-off)</td>
</tr>
<tr>
<td>DA Neurons</td>
<td>moderate rate</td>
<td>moderate rate</td>
<td>moderate rate</td>
</tr>
<tr>
<td>VLPO Neurons</td>
<td>inactive</td>
<td>highest rates</td>
<td>inactive</td>
</tr>
<tr>
<td>REM-on Neurons</td>
<td>inactive</td>
<td>inactive</td>
<td>high rate</td>
</tr>
<tr>
<td>Orexin Neurons</td>
<td>high rate</td>
<td>low rate</td>
<td>low rate</td>
</tr>
</tbody>
</table>
In mammals, REM sleep and NREM sleep are **ACTIVE** processes mediated by the increased activity of, respectively, pontine REM-on neurons and VLPO NREM-on neurons.

ACh neurons are responsible for desynchronized EEG / LFP of waking and REM sleep – they fire more slowly in NREM.

VLPO neurons are unusual in firing faster during NREM sleep as compared to waking – some continue firing in REM sleep.

narcoleptic humans lack orexin neurons

Aside from generating changes in brain activity associated with REM sleep and driving eye movements and twitches, REM-on neurons also mediate trunk muscle atonia that accompanies REM sleep. REM behavior disorder is associated with ‘acting out’ dreams and can be mimicked by lesions of the pons.
slow-waves (delta waves, 0.5-4 Hz) and spindles (12-16 Hz) that define NREM sleep are a reflection of burst-pause activity patterns of thalamic and cortical neurons – burst-pause activity results from the ‘deinactivation’ of $I_h$ and $I_t$ voltage-gated ion channels and their interaction with Ca++-dependent K+ channels – the former are deinactivated only when membrane potentials reach a certain level of hyperpolarization ($<-65$ mV) are depolarizing influences which counteract the hyperpolarizing influence of the Ca++-dependent K+ channel during waking, NE, 5-HT, and ACh all cause certain K+ channels (K+ ‘leak’ channels) to close – this depolarizes thalamic and cortical neurons tonically and renders $I_h$ and $I_t$ Ca++ channels inoperative because the membrane potential never gets hyperpolarized enough to deinactivate them during REM sleep, ACh by itself depolarizes thalamic and cortical neurons during NREM sleep VLPO neurons likely inhibit ACh neurons
ontogeny: timing and amount of different types of sleep changes across the lifespan

phylogeny follows ontogeny (for the most part): animals that are born relatively under-developed, like ferrets, exhibit higher amounts of overall sleep (especially REM sleep) as compared to animals, like horses, born relatively developed……but, if sleep is important for development, why does it persist into adulthood?
NREM sleep is associated with reduced brain metabolism and sleep amounts tend to vary inversely with body size which, in turn, is negatively correlated with metabolism....why, then, is there REM sleep where metabolism is very high?
for a period of an hour or so, activity patterns across multiple neurons resemble, in sleep, activity patterns seen in prior waking – this has been interpreted to suggest: 1) that memories are consolidated in sleep; and 2) based on the transient nature of the phenomenon, to suggest that synaptic strengths across the brain are decremented during sleep (i.e., that sleep is for forgetting)……yet sleep is not absolutely necessary for learning.
the function of sleep: closing considerations

why REM and NREM sleep and why do they cycle?

could sleep have many functions within one animal?

could sleep have different functions across animals?

is sleep actually necessary?