Terms you should encounter along the way

frequency, pitch, amplitude, loudness, timbre, complexity, frequency X power (i.e., amplitude), compressed vs. rarefied air, pinna, malleus, incus, stapes, tympanic membrane, oval window, cochlea, height localization of sound source, middle ear muscles, hair cell, basilar membrane, tectorial membrane, cochlear ganglion cell, cochlear nucleus neuron, stereocilia, kinocilium, Fourier transform, tonotopic map, preferred frequency, auditory response field, medial geniculate body, lateral superior olivary nucleus, medial superior olivary nucleus, interaural time difference (ITD), interaural level difference (ILD), order-dependent responses / temporal ordering of sounds, echolocation, constant frequency component (CF), frequency modulated component (FM), target distance, target size, target location, target velocity, delay specific activation (area 4 of bat cortex), Doppler shift (i.e., CF pitch shift)

ionotropic receptors, metabotropic receptors, 2nd messenger responses, neuromodulatory neurotransmitter, norepinephrine (NE) / locus coeruleus, serotonin (5-HT) / raphe nuclei, acetylcholine (ACh), histamine (HA), dopamine (DA) / ventral tegmental area / substantia nigra, phosphorylation, ion channel state, ion channel kinetics, Ca++-dependent K+ channels, current steps mimicking excitatory input, pyriform cortex, intrinsic vs. extrinsic input, Alzheimer's disease, depression, schizophrenia, parkinson's, attention deficit disorder

hippocampus, dentate gyrus (DG), CA3, CA1, convergence, divergence, reentry, egocentric frame of reference, arbitrary frame of reference, allocentric, object-centered, route-centered, head direction cells, anterodorsal thalamic nucleus, XY vs. polar plot for head direction association with firing rate, grid cell, tessellated triangles, grid and head-direction cells, velocity-dependent firing rates, place cell, color ratemap, 'where' pathway, parietal cortex, area MST/MT, area 7a, area VIP, spatial imagination

pontine nuclei, granule cells, Purkinje cells, cerebellar nuclei, parallel fibers, Purkinje cell dendritic tree, fastigial nucleus, interpositus nucleus, dentate nucleus, putamen + caudate = striatum, globus pallidus internal segment (GPi), globus pallidus external segment (GPe), substantia nigra, direct pathway, indirect pathway, hyperdirect pathway, medium spiny neurons, D1 dopamine receptors, D2 dopamine receptors, reward expectation vs. actual reward, saccade latency vs. expected reward

local field potential (LFP), sleep spindles, slow-waves (delta waves), sawtooth waves, rapid-eye-movement sleep (REM), non-rapid-eye-movement sleep (NREM), muscle tone, heart rate, mentation, NREM-REM cycle time, sleep deprivation, sleep propensity, circadian, factor 'S' – the homeostatic component of sleep, VLPO neurons, REM-on neurons, orexin neurons, active induction of sleep, narcoleptic, REM-behavior disorder, Ih and It Ca++ channels, K+ leak channels, sleep and development, sleep and metabolism, sleep and learning.
Principles

‘Active sensing’: Much of our experience of the environment is driven by the ways that we direct our senses. For example, our perception of the visual world depends greatly on our choices as to where to direct our eyes. The bat goes a step further by sending out information (calls) that it knows will result in valuable information as to the location of objects in the environment.

‘Functional anatomy’: The vast majority of the brain is composed of connections between neurons releasing glutamate or GABA which produce relatively short (10’s of ms) depolarizations or hyperpolarizations through the activation of ligand-gated ion channels (ionotropic receptors). A much smaller population of neurons, the neuromodulators, release NE, 5-HT, DA, ACh, or HA to widespread regions of the brain. Through the action of such neuromodulators via metabotropic receptors, the properties of voltage-gated ion channels are altered over relatively long periods of time (100’s of ms). The alteration of voltage-gated ion channels in turn alters the degree to which glutamate or GABA depolarize or hyperpolarize the cell. In this way, the ‘anatomy’ of the brain (connections between glutamate and GABA neurons), while physically stable, is ‘functionally’ changed according to the influence of neuromodulators. Any particular part of the brain may operate differently depending on the action of neuromodulators.

‘Frames of reference’: Any point in space is defined only by its relation to other points in space. This is essential to remember when examining the spatial specificity of neuronal activity. In what reference space is its activity spatially specific?

‘Reentry’: This refers to the general property of connections among brain regions. Rather than a linear, unidirectional flow of information between structures as in A → B → C → D, the brain utilizes re-entrant connections. C and D may, for instance, project back onto A and/or B. This has the consequence that B’s response to A at time point X will be impacted by C’s response to B at time point X-1. Reentry mixes information across time in the same way that convergent connections onto a single neuron mix the information contained in the input neurons.

‘Homeostasis’: A variable (e.g., sleep amounts or temperature) is said to be homeostatically regulated (i.e., to be in homeostasis) when a system detecting its value adopts measures to keep that value within a certain small range (i.e., in and around a ‘set’ point). By monitoring of the brain’s attempts to maintain a set point for sleep amounts over the day, one can potentially define the chemical constituents or brain activity patterns that register sleep need or fulfillment of sleep need. This may then begin to define a potential function for sleep itself.
Tables

What can a bat tell from an echo and what type of information does it use?

Characteristics of brain neuromodulatory systems.

Egocentric vs. arbitrary frames of reference

Shared properties of large reentrant systems (the hippocampus, basal ganglia, and cerebellum)

Cerebellar function as viewed via the properties of individual cerebellar nuclei

Sleep characteristics (comparing the features of different sleep/wake states and comparing the firing activity of neurons across sleep/wake states)
Concepts

Characterization of sounds through graphing of amplitude (or 'power') at different frequencies. Also known as the 'spectrograph'

Frequency-dependent sound amplification.

The basilar membrane as a Fourier transform

Topographic representation of sound (tonotopy)

Defining the 'response field' of an auditory system neuron

Mapping of sound amplitude in primary auditory cortex

Order-dependent responses to pure tones

Constant frequency vs. frequency-modulated components of bat calls

The Doppler effect

Ionotropic vs. metabotropic receptors

Mapping of position in space

Expected vs. actual reward – the difference used as a signal to maintain an action and/or make that action more robust

LFP oscillations as reflecting common modulation (hyperpol. / depol.) of a population of neurons

Sleep depth defined behaviorally (arousal threshold) and through cortical LFP (percentage slow-waves)
## Basic Characterization of Sound Waves

<table>
<thead>
<tr>
<th>Physical Dimension</th>
<th>Perceptual Dimension</th>
<th>Power (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (intensity)</td>
<td>Loudness</td>
<td>( \text{log} S(f) ) (dB)</td>
</tr>
<tr>
<td>Frequency</td>
<td>Pitch</td>
<td>1.0 - 5.0 kHz</td>
</tr>
<tr>
<td>Complexity</td>
<td>Timbre</td>
<td></td>
</tr>
</tbody>
</table>

- **Loudness**: Represented by waveforms indicating different intensities.
- **Pitch**: Reflects frequency differences with waveforms showing low and high pitches.
- **Timbre**: Demonstrates complexity with simple and complex waveforms.

![Graph showing power (dB) over frequency](image)}
outer ear (pinna) shape reflects sound from different sources in different ways providing a possible source for localization of the height of a sound source
middle ear bones amplify sound in a frequency-dependent fashion

frequency-dependence of amplification is, in turn, modulated by middle ear muscle contractions
basilar membrane vibration is transduced into neural signals by hair cells
the inner ear – transformation of pressure waves (sound) and their frequency characteristics (spectra) into neural signals
varying stiffness of the basilar membrane results in a Fourier transform of the vibrations of the endolymph
segregation of cochlear ganglion cell outputs to cochlear nucleus according to the position of their hair cell inputs – creation of a topographic representation of sound (tonotopy) that ultimately reaches primary auditory cortex
Hair cell deflections toward the kinocilium generate greater depolarizations than comparable deflections away from the kinocilium generate hyperpolarizations.

Because of this, hair cells in regions of the basilar membrane oscillating at high frequencies exhibit non-oscillating depolarizations in response to high frequency sounds.
cochlear nucleus neurons exhibit heterogeneous responses to inputs from ganglion cells. The response fields of each are described in frequency X amplitude response plots.
Lec8_02022010 – the auditory system II – timing is everything
principle of the week – ‘active sensing’
ascending pathways of the mammalian auditory system
the ‘where’ of sound – sound source localization by comparison of inputs to the left and right ears

interaural time difference (ITD)

not useful for persistent high frequency sounds (>2000 Hz) as hair cell responses do not oscillate in response to high frequency tones

interaural level difference (ILD)

not useful for low frequency sounds as their amplitude is less impacted by the head

what about sound source height?
brainstem processing of auditory information yields sound source localization

the organization of cochlear nucleus outputs to the brainstem yields responses to interaural time differences in medial superior olive neurons and interaural level differences in lateral superior olive neurons.
Timing of spikes in A1 can be very consistent even for highly complex auditory sequences.
multiple sub-regions of auditory cortex: most contain a tonotopic map – responses to different sound intensities are heterogenous
timing matters: A1 responses to pure tones are modulated by the frequency ordering of preceding tones.

A1 preferred frequency map (tonotopy)

preferred frequency = pitch for which amplitude necessary to give a response is lowest

A1 preferred ‘sweep direction’ map

preferred direction = ordering (low→high vs. high→low) of frequencies in a frequency sweep that produces the strongest response to the preferred frequency.
history-dependence of A1 response fields: order-dependent excitation
history-dependence of A1 response fields: order-dependent suppression
temporal dependence of response to preferred frequencies means that auditory ‘objects’ can be registered by the patterns of firing of A1 neurons.

vocalization of a monkey can be considered an auditory object (similar, in principal, to a spoken word).

both the ordering of tones and their temporal relationships alter A1 responses.
bat echolocation: finding and tracking the location of prey through comparison of sound time signatures
What Can the Bat Tell from an Echo?

Distance to target – FM delay

Absolute target size - amplitude

Azimuth and elevation- ITD, ILD

Velocity of target- CF Doppler shift

Flutter of target (i.e., wing beat) – modulation of echo delay
The stiffness of the basilar membrane is at its maximum at frequencies around 60 kHz to 62 kHz, which is optimal for membrane oscillation.
target proximity: utilization of the FM component delay

bat cortex area 4 contains neurons which recognize the FM component of a call AND register its delay from the time of the call
target speed: utilization of changes in pitch of the CF component between call and echo (i.e., detecting the Doppler shift in frequency)
take-homes:

• A1 neurons respond best to sounds at particular frequencies, but those responses can vary greatly according to:
  • sound amplitude – neurons may exhibit a linear increase in response to increasing amplitude of a preferred-frequency tone or may exhibit highest firing at some intermediate amplitude and less at lower and higher amplitudes
  • the temporal ordering of sound – neurons may exhibit very different responses to a preferred-frequency tone depending on the tones that precede and accompany it

• the basilar membrane of a bat has extra space devoted to regions responding to sounds near 60 kHz (in the range of its calls) – in this sense, it can be considered the bat’s auditory fovea

• bats use long ‘CF’ calls to assess Doppler shift and, in turn, the movement speed of their prey

• bats use shorter ‘FM’ sweeps to assess their proximity to their prey

• prey size can be determined by the echo amplitude (closer = louder)
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 diagram]
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

- **Cholinergic (ACh) system**: Pontine and basal forebrain groups
- **Dopamine (DA) system**: Ventral tegmental area and substantia nigra area (both in midbrain) – note more localized projections
- **Norepinephrine (NE) system**: Main nucleus is the ‘locus coeruleus’ in the pons
- **Histamine (HA) system**: The ‘forgotten one’ – neurons localized to posterior hypothalamus
- **Serotonin (5-HT) system**: Several ‘raphe’ nuclei distributed in brainstem
examples of metabotropic pathways by which neuromodulators affect target neurons: the cyclic-AMP and phosphoinositide (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 agonist application (i.e., activation of ACh receptors)

current injection

ACh agonist application (i.e., activation of ACh receptors)

increasing current injection steps

persistent firing rate response to short-term excitatory input

K+ efflux in response to depolarizing current step

change in membrane potential in response to neuromodulatory inputs is sometimes minimal

persistent firing response may, in turn, be modulated by number of excitatory inputs

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)

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

drugs of abuse associated with neuromodulatory systems:

- ACh: nicotine
- 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
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?
MAPPING SPACE IN THE BRAIN – RULE 2: DEFINE THE FRAME OF REFERENCE

egocentric frames
- retinal space
- eye position
- hand space

arbitrary frames
- allocentric (world-centered)
- route-centered
- object-centered

senses

musculature
tracking directional heading in the allocentric (world-centered) frame of reference: ‘head direction’ cells
– firing is tuned to the orientation of the animals 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
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.

Sargolini et al., Science, 2006
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
parietal cortex neurons in behaving rats map path segments (e.g., start pt. to first R turn)

Nitz, Neuron, 2006
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
BOLD SIGNALS IMPLICATE HIPPOCAMPUS AND PARIETAL CORTEX
IN NOVEL SCENE CONSTRUCTION

Hassabis et al., JNS, 2007
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)

**Cerebellum**
- Granule Cells
- Purkinje Cells
- Cerebellar Nuclei (base of cerebellum – each contains homunculus)

**Vestibular and Proprioceptive Inputs**

**Inferior Olive**
- Climbing Fibers - ‘error’ signal induces learning

**Convergence**
- Coordination across muscles of the body

**Divergence**

**Ventrolateral Thalamus**
- (And brainstem and spinal cord)

**Motor Cortex**

**ACTIONS**
- Convergence
- Divergence
**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>Nucleus</th>
<th>Function</th>
<th>Neuronal Activity</th>
<th>Localized Inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fastigial nucleus</td>
<td>Postural adjustments</td>
<td>Eye movements / walking</td>
<td>Posture and gait instability</td>
</tr>
<tr>
<td>Interpositus nucleus</td>
<td>Balance of agonist / antagonist muscles</td>
<td>Perturbation of limb/body from holding position</td>
<td>Tremor</td>
</tr>
<tr>
<td>Dentate nucleus</td>
<td>Reaction time delays; poor endpoint control</td>
<td>Auditory and vision triggered movements</td>
<td></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.

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

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

the thalamic sub-region associated with the basal ganglia output is the ‘ventrolateral’ thalamus

together the caudate and putamen are called the ‘striatum’
cortex → basal ganglia → cortex: direct, indirect, and hyperdirect pathways

- 2/3's of output to prefrontal, premotor or motor cortex
- Convergence: all regions of cortex contribute
- Direct pathway
- Indirect pathway
- Hyperdirect pathway
- GABA, enkephalin, D2
- GABA, substance P, D1

Brainstem

Caudate/ Putamen

GPe

GPI/SNr

STN

Striatum

Cortex

SNc/VTA

Thalamus

Convergence

Divergence
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)

DA neuron firing rate

actual – predicted reward value

baseline rate

[Diagram showing the direct and indirect pathways involving cortex input, SNpc – DA input to D1/D2, and GABA output to GPi/GPe]

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).

The direct pathway involves cortex input, SNpc – DA input to D1, and GABA output to GPi. The indirect pathway involves cortex input, SNpc – DA input to D2, and GABA output to GPe. Both pathways are modulated by DA neuron activity.
entire neocortex: combined motor and sensory context

‘motor’ neocortex: implementation of decision

‘indirect’ pathway—favored by low DA levels

‘direct’ pathway—favored by high DA levels

strong inhibition → weak inhibition

strong excitation → weak excitation

striatum →

GP external →

GP internal →

thalamus →
basal ganglia also appears to determine the robustness of a response

reward expectation drives changes in latency to onset of a saccade following cue onset

antagonists of DA type D1 and D2 receptors differentially affect latency differences

different caudate neurons exhibit saccade related activity dependent on reward expectation (panel 1), on expectation of no reward (panel 2), or pre-saccade activity dependent on saccade type AND reward expectation (panel 3)
principle: ‘homeostasis’

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.
‘functional anatomy’ –

Even when the strength of a synaptic connection between two neurons is stable (i.e., release of transmitter by the presynaptic neuron opens the same number and type of ionotropic receptors on the postsynaptic neuron), the impact of the presynaptic neuron on the postsynaptic neuron’s membrane potential and rate of action potentials may differ depending on the properties of other types of ion channels. The properties of those other ion channels may vary dynamically across time. In this sense, the ‘connection’, in terms of its influence on the postsynaptic neuron, varies across time. The ‘anatomy’ varies as a ‘function’ of other variables such as the properties of non-ligand-gated ion channels.

The properties (e.g., state, kinetics, distribution) of those other ion channels may be impacted by a number of different factors including gene expression and the release rate of neuromodulatory neurotransmitters (e.g., NE, HA, ACh, DA, 5-HT). That is, the neuromodulator may change the ‘functional anatomy’ of the brain. For example, when neuron A (presynaptic), having fired an action potential, releases the neurotransmitter glutamate onto neuron B (postsynaptic), ionotropic receptors are activated resulting in influx of Na+ and Ca++ ions into neuron B (a depolarizing influence). The level of actual depolarization (size of the EPSP) can be affected by the presence of other types of ion channels such as the Ca++-dependent K+ channel. This channel opens when Ca++ concentration in the neuron is relatively high (as when many glutamate receptors are activated at one time). When the Ca++-dependent K+ channel is activated (open), K+ efflux effectively produces a hyperpolarizing influence (positive K+ ions leave the neuron) which counteracts the depolarizing influence of the Na+ and Ca++ ion influx. If, as in one of our examples, a neuromodulator, through a 2nd messenger system, activates a protein kinase which phosphorylates the Ca++-dependent K+ channel, the kinetics (open time) of the channel may be altered. In the example (drawing on the Desai and Walcott paper), ACh causes the open-times of Ca++-dependent K+ channels to shorten. In the absence of excitatory input, this has no effect on the membrane potential as this type of channel is not active at rest. However, when an excitatory input and its associated Ca++ influx arrives, the hyperpolarizing counteraction brought by the Ca++-dependent K+ channel is of a shorter duration allowing the neuron to be depolarized to action potential threshold for a greater proportion of the time associated with the excitatory input. Thus, because of the action of the neuromodulator, the neuron responds differently to the same input.

In our second example (Hasselmo et al), the specific ion channel, unfortunately, has not been identified. Both NE and ACh are found to alter the response to excitatory inputs to layer Ib more so than layer Ia. Since those excitatory inputs are known to arise from different sources (olfactory bulb / extrinsic vs. other cortical areas / intrinsic), this means that the same layer II neuron, with dendrites in both Ia and Ib, responds more to Ia inputs when ACh and/or NE release is high. This is another example of ‘functional anatomy’. The likely explanation is that the ion channels impacted by ACh and NE are distributed differently (e.g., higher concentration in Ib where more change takes place). Another possible explanation is that ACh and NE receptors themselves are distributed unevenly.
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?

at any given time, sleep propensity is thought to be related to the difference between two components (S minus C):

1) a circadian component (C above)

2) an ‘S’ component which reflects the homeostatic component of sleep propensity

adapted from Trachsel et al., AJP, 1986
<table>
<thead>
<tr>
<th>sleep characteristics:</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>hippo. 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>
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</table>
The pons is both necessary and sufficient for the induction of REM sleep. Lesions targeting sites of REM-on neurons produce permanent and selective suppression of REM sleep. REM-on and some REM-off neurons (NE and 5-HT) are localized in the same sub-region of the pons. Stimulation of REM-off neurons will also suppress REM sleep. In REM, REM-off neurons lack excitatory input from orexin neurons and are actively inhibited by GABA neurons whose locations are unknown.
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.

**NE neurons**
- Activity increases in response to unexpected events.

**5-HT neurons**
- Activity is tightly linked to overall degree of movement.

**HA neurons**
- Narcoleptic humans lack orexin neurons.

**REM-on 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 de-inactivate them

during REM sleep, ACh by itself depolarizes thalamic and cortical neurons

during NREM sleep VLPO neurons likely inhibit ACh neurons
sleep function I: the development argument

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 positively 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?