terms you should encounter along the way:

Donald Hebb, convergence, divergence, synaptic efficacy, plasticity, synaptic potentiation, synaptic depression, long-term potentiation, long-term depression, synapse shape, ionotropic receptors, co-activity pattern, fragile-X mice, mental retardation, mature vs. immature synaptic spine, spike-timing dependent plasticity, neuromodulatory systems, Pavlovian fear conditioning, association (associative learning), foot-shock, freezing, conditioned stimulus, unconditioned stimulus, lateral amygdala, central amygdala, labile memories, extinction

procedural memory, declarative memory, episodic memory, working memory, associative memory, reach-to-grasp task, ‘more is better’, ACh-dependent alteration of motor cortex and auditory topographic representations, motor skill learning, perceptual skill learning, place strategy vs. response strategy, training stage dependent strategy, relative ACh release in hippocampus and basal ganglia, retrospective place coding, prospective place coding, 7+/−2, ‘delay’ task, delay activity, cue+delay activity, delay+action activity, prefrontal-dependent delay activity in parietal cortex

intrafusal muscle, extrafusal muscle, tendon, ventral vs. dorsal spinal cord, slow-twitch vs. fast-twitch muscle fibers, motor neuron, motor cortex neuron, muscle synergies, spinal cord interneuron, motor cortex neuron directional tuning, robo-monkey, premotor cortex, premotor action-specific activity, premotor planning activity, premotor sequence-dependent activity, premotor mirror activity

prefrontal cortex, attention, episode ‘marking’, interval tracking, counting, category mapping, efferent projections of prefrontal cortex, enhancement vs. suppression of stimulus induced activity through attention, conditional probability, pop-out (bottom-up) attention vs. top-down (search) attention
principles of the week:

fire together – wire together:
This pertains to the idea that the strength of a connection between a presynaptic and postsynaptic neuron (measured by examining the degree of depolarization in the postsynaptic neuron resulting from a single action potential in a presynaptic neuron) can change (i.e., wire together) as a function of whether or not the two neurons are co-active (i.e., fire together).

implicit vs. explicit memory:
There are many types of memory (associative, procedural, declarative, episodic, working). For some types (declarative, episodic), it is possible to consciously know the content of the memory (for example, the sky is blue or “I ate breakfast at Denny’s this morning”) while, for others, it is not consciously known what the memory is exactly (as in procedural memories like remembering how to swim – a motor skill memory).

the population code:
This pertains to the idea that perceptions (e.g., awareness of present spatial position) and actions are both realized by ‘patterns’ of activity among large populations of neurons as opposed to activation of single neurons. With respect to the motor system, the population firing rate vector (a list of the firing rates for a large set of motor cortex neurons) bears direct relation to the present on-going action (itself a pattern of muscle synergies).

top-down processing:
This pertains to the idea that structures such as the prefrontal cortex may, to some extent, control or bias activity patterns in other brain structures. Prefrontal cortex may, for instance, be responsible for delay activity in the parietal cortex. Similarly, prefrontal cortex can control ACh release in structures such as the visual cortex thereby changing how the visual cortex responds to visual input.
concepts:

plasticity
synaptic ‘efficacy’ or synaptic ‘strength’
spike timing dependent plasticity ‘curve’
conditioned vs. unconditioned stimulus
‘labile’ memories
‘types’ of memories
strategy competition
‘delay’ or ‘working memory’ activity
prefrontal control of delay activity in parietal cortex
muscle ‘synergy’
action ‘related’ activity that doesn’t reflect actual motor actions (e.g., mirror neurons)
attention enhancement vs. suppression of stimulus-induced activity
conditional probability (the ‘hazard function’)

‘tables’:

1. listing of information pertaining to the features of plasticity in synaptic strengths (or efficacy) – third slide of lecture 14.
2. properties of spinal cord interneurons
3. indirect roles of premotor cortex in motor control
4. forms of prefrontal firing that reflect abstract variables (e.g., time or category)
"The general idea is an old one, that any two cells or systems of cells that are repeatedly active at the same time will tend to become 'associated', so that activity in one facilitates activity in the other." (Hebb 1949)

"When one cell repeatedly assists in firing another, the axon of the first cell develops synaptic knobs (or enlarges them if they already exist) in contact with the soma of the second cell." (Hebb 1949)
Learn – if sensory cell 1 AND 3, then action 2 = reward
changes in synaptic efficacy can reflect either changes in depolarization caused by increases or decreases in the amount of neurotransmitter released by an action potential (presynaptic change) and/or increases or decreases in the amount of response of the postsynaptic neuron to the same amount of glutamate released by the presynaptic neuron.

Post-synaptic changes usually reflect changes in the shape of the synapse, changes in the number of ionotropic receptors, changes in the kinetics of ionotropic receptors, and/or development or retraction of contacts (synapses) between neurons.

Changes in synaptic efficacy often depend on the timing and/or amount of co-activity between two neurons (as in ‘fire together, wire together’).

For any two connected neurons, the co-activity rules for synaptic change may differ greatly.

Co-activity leading to changes in synaptic efficacy may depend on the presence or absence of a third party such as a neuromodulator or a peptide.

Synaptic potentiation (as in figure) and synaptic depression are changes in the amount of depolarization in a post-synaptic neuron when an input neuron (presynaptic) releases neurotransmitter following an action potential – such alterations in depolarization amount are termed changes in ‘synaptic efficacy’.
visualization of potentiating, depressing, and unchanged synapses following stimulation of hippocampal CA3 inputs into CA1 region of hippocampus

Becker et al., Neuron, 2008

Dendritic spines of cortical neurons in fragile-X mice (mental retardation) are longer / immature

Dolan et al., Neuron, 2007

Potentiation

Deression

Unchanged

mature synaptic spine

immature synaptic spine
Spike timing dependent plasticity: changes in synaptic ‘efficacy’ between two neurons (one presynaptic, the other postsynaptic) related to the relative timing of their action potentials.

- Post-synaptic neuron fires before pre-synaptic neuron ($\Delta t < 0$)
- Pre-synaptic neuron fires before post-synaptic neuron ($\Delta t > 0$)

Diagram:
- Intracellular electrode for recording of synaptic potentials and action potentials or for stimulation of an action potential.
- Synaptic potential in post-synaptic neuron resulting from a single presynaptic spike.
- Synaptic depression (or depotentiation).
- Synaptic potentiation.

Graph:
- X-axis: Spike timing (msec)
- Y-axis: Synaptic change (%)
co-activity rules for synaptic efficacy change depend on neuromodulatory systems

- no ACh, no NE (as in NREM sleep)
- ACh + NE (as in waking)
- NE, no ACh (??)
- ACh, no NE (e.g., REM sleep)
learning 101: Pavlovian fear conditioning – association of an initially neutral tone (CS) with a foot-shock results in ‘freezing’ responses when the tone alone is played.

Auditory cortex / Auditory thalamus (neurons excited by sound stimulus - CS)

Somatosensory cortex / Somatosensory thalamus (neurons excited by shock stimulus - US)

Hippocampus (place information)

IT (visual item information)

Lateral amygdala

Central amygdala

Before pairing

After pairing

Freezing response, increased heart rate, etc.
re-remembering: memories in the amygdala are ‘labile’ – their recall makes them vulnerable to erasure or consolidation

Doyere et al., NN, 2007

shock associated with 2 different CS’s

introduce drug that blocks potentiation (U0126)

prior to drug, increased freezing to both tones following pairing with shock (standard fear conditioning)

after drug, reduced freezing to only the tone that was replayed

Doyere et al., NN, 2007
curing PTSD by taking advantage of the ‘labile’ nature of some memories:

Day 1: Humans develop eye-blink responses to tones (the conditioned stimuli - CS) paired with shocks (the unconditioned stimuli – US).

Day 2: Two groups are exposed to the CS after having been given placebo (top graphs) or propranolol (middle graphs), a compound that blocks the action of norepinephrine (NE). A third group is given propranolol, but not exposed to the CS.

Day 3: An set of ‘extinction’ trials (presentation of CS in absence of US) is given and eye-blink responses are recorded. Blocking the action of NE on day 2 is shown to have the effect of ‘erasing’ the CS-US association.

Day 4: Usually, as in the placebo condition, the US given alone reverses the extinction of the CS-US association that was achieved on day 3. Blocking the action of NE on day negates this.
the term ‘procedural knowledge’, sometimes called implicit memory, denotes knowledge of how to accomplish a task, and often pertains to knowledge which unlike ‘declarative knowledge’ cannot be easily articulated by the individual, or knowledge that is nonconscious.
Co-activity rules for synaptic efficacy change depend on neuromodulatory systems.

- **No ACh, no NE (as in NREM sleep)**
  - **NE, no ACh (??)**

- **ACh + NE (as in waking)**
  - **ACh, no NE (e.g., REM sleep)**
learning 101: Pavlovian fear conditioning – association of an initially neutral tone (CS) with a foot-shock results in ‘freezing’ responses when the tone alone is played – this type of memory may be implicit or explicit.
rats learn, across days, to efficiently reach and grasp a small sugar pellet over those days, the muscle patterns used in grasping adapt

over those days, the area of primary motor cortex taken up by neurons associated with the reaching limb grows

if ACh inputs to the primary motor cortex are removed, neither the learning nor the changes in motor cortex occur

**Kargo and Nitz, JNS, 2003**

**mod. from Conner et al., Neuron, 2003**
rats trained to make a nosepoke if they detect a 4 kHz tone show improvements in detection over days of training.

Over the same time period the topographic representation of pitch in primary auditory cortex changes such that more neurons respond to 4 kHz tones.

In separate experiments, pairing of a 9 kHz tone with stimulation of ACh neurons in the basal forebrain changes the topographic representation in primary auditory cortex such that more neurons respond to 9 kHz tones.
in training (below), the rat is taught to move to the goal to obtain reward

subsequently, on test trials (above), the maze is turned upside-down and the rat demonstrates whether he has learned to ‘make a left’ at the ‘T’ (a response strategy) or to ‘move to that place in the room’ (a place strategy)

if the rat is asked this question early in training (within the first couple of days), one tends to see a ‘place’ strategy and ACh is high in the hippocampus

if the rat is asked this question late in training, one tends to see a ‘response’ strategy and ACh is high in the basal ganglia

early in training, when one would normally expect a ‘place’ strategy, inactivation of the hippocampus (the home of ‘place cells’) results in the emergence of a response strategy

late in training, when one would normally expect a ‘response’ strategy, inactivation of the basal ganglia (proposed to select responses via the direct pathway) results in the emergence of a place strategy

thus, the animal has learned two separate strategies which compete for expression
episodic memory (memory for events and their ordering - a form of explicit memory):

hippocampal cell activity in a ‘place’ often depends on the places previously or subsequently visited (this is termed retrospective and prospective place coding)

about half of all hippocampal neurons fire spikes (green dots) when the animal is in a certain part of the maze (here the S arm) – this is seen irrespective of the direction taken after reaching the middle

some hippocampal neurons fire in a certain place, but only if they reached that place from the N as opposed to the S side – their activity depends on the character of the full episode and is termed ‘retrospective’

other hippocampal neurons are ‘prospective’ – they fire in a certain place depending on where the animal will go from that place – they too have activity dependent on the full episode

for one block of trials, the animal must travel to the west end when placed at either the N or S start point

for the next block, the animal must travel to the east end when placed at either the N or S start point

adap. from Ferbinteanu and Shapiro, Neuron, 2003
working memory: holding items in memory (7+/−2) is achieved through interaction of the prefrontal and parietal cortex
an example: prefrontal ‘top-down’ influences on parietal cortex during an oculomotor delayed response task – inactivation of prefrontal cortex via cooling depresses ‘working memory’ responses of parietal cortex neurons and increases errors

Chafee and Goldman-Rakic, JNP, 2000
principle of the week: the population code

“they’ll fix you…they fix everything” - Robocop
motor neurons and muscle fibers: one motor neuron → one muscle, but to many fibers (but all of the same type)

- slow-twitch: 50 ms to peak force, relatively small force, non-fatiguing (aerobic), useful for tonic movements as in maintaining posture, innervated by type S motor neurons

- fast-twitch: 25 ms to peak force, large force, fatigue easily (glycolysis), useful for quick powerful movements. (jerk), innervated by type F motor neurons capable of high firing rates
common, repeatedly utilized behaviors such as walking, chewing, withdrawal (e.g., a finger from a hot stove) imply the workings of central pattern generators - these are, in turn, formed of muscle ‘synergies’ that evolve over time.

Activation / inactivation patterns of muscles at any given time are ‘synergies’ (e.g., knee and hip extensor muscles contract while ankle and knee flexors relax at time given by red arrow).

Kargo and Nitz, JNS, 2003
a second look at the knee-jerk reflex (versus normal muscle activation) – spinal cord interneuron networks coordinate different muscle activation / inactivation patterns

the knee-jerk reflex – dorsal root ganglion cells responding to muscle spindle afferents activate the ‘agonist’ muscle (quadriceps) while inactivating an ‘antagonist’ muscle (hamstring) through an inhibitory interneuron

but…..activation of the hamstring will stretch the patellar tendon connecting the quadriceps to the tibia (and activate the golgi tendon organ)…..so what about situations where activation of the hamstring is required?

answer: inputs from, for instance, motor cortex which drive hamstring contraction through motor neurons also inhibit dorsal root ganglion cell inputs to the quadriceps muscle by hyperpolarizing the presynaptic terminal (thereby preventing transmitter release)
motor control involves the selection of muscle synergies by several different systems

corticospinal (motor cortex output)
vestibulospinal
reticulospinal (mesencephalic locomotor region)
rubrospinal (receives output from cerebellum)

spinal cord interneurons:
1. can be excitatory (green) or inhibitory (red)
2. are interconnected with themselves and motorneurons
3. may have axons which cross the commisure and/or extend into other segments
4. are recipients of both converging and diverging motor cortex inputs
convergence AND divergence of corticospinal axons

single motor cortex neurons projecting to the spinal cord exhibit divergence of their axon terminals to motor neurons of the ventral spinal cord that, in turn, innervate different muscles (i.e., a single motor cortex neuron can activate several different muscles)

spike-triggered recordings of six muscles of the forearm

neighboring regions of motor cortex (e.g., thumb and forefinger)

projections of motor cortex neurons converge onto single spinal cord motor neurons (e.g., ‘thumb’ and ‘forefinger’ regions of the motor homonculus may form synapses on the same motor neuron)
defining the patterns produced by population firing rate vectors

action potential rasters (tic marks) for a single neuron during 5 separate reaches to eight different directions from the center point – this neuron fires the greatest number of action potentials for the south and southeast reaches (red line indicates preferred direction)

across a population of motor cortex neurons, each will have a different preferred direction – by considering the firing rate of all recorded neurons at any given time (i.e., the population rate vector), the associated direction of movement can be predicted
robo-monkey: interfacing the activity patterns of monkey motor cortex neurons with a robot arm – monkeys learn to generate activity patterns that will control a robot arm

robot arm & ‘fingers’ pinching a piece of food – monkey subsequently moves food to mouth
controlling the controller: premotor cortex drives activity patterns in motor cortex and is, in turn, driven by both prefrontal and parietal cortices
dissociating the premotor and motor cortex I: premotor cortex in navigating rats exhibits more abstract relationships to action – mapping of action, sequence-dependence of action mapping, and mapping of action plans.

sequence-dependent action mapping: this neuron fires after the last turn if it’s a right turn.

action planning: this neuron fires during forward locomotion preceding right turns.

action mapping: this neuron fires during the execution of any right turn.
dissociating the premotor and motor cortex II: activity may reflect the position of an action in an action sequence

activity of a single premotor neuron which fires over the final segment / action irrespective of the direction of movement

activity of single premotor neuron which fires over the first segment / action irrespective of the direction of movement
dissociating the premotor and motor cortex III: ‘mirror neurons’ of the premotor cortex – activity maps actual as well as witnessed behaviors of the same type

right: a neuron in premotor cortex fire during grasping AND as the monkey watches someone else do the same thing

below: a neuron in premotor cortex fires when the monkey breaks a peanut (M), when he sees and hears someone else do the same (V+S), when he only sees it (V), and when he only hears it (S)

below-right: a neuron in premotor cortex fires when an object is grasped even if the object is hidden by a screen (but known to be in place)
William James, in his monumental *Principles of Psychology* (1890), remarked:

“*Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others, and is a condition which has a real opposite in the confused, dazed, scatterbrained state which in French is called distraction, and Zerstreutheit in German.*”
premotor cortex – a more indirect role in motor control

1. activity, as in primary motor cortex, may directly reflect present action

2. activity accompanies actions as well as planning for actions

3. action-related activity may depend on ordering of actions in a sequence

3. activity may reflect perceived actions as opposed to actual movements (as in ‘mirroring’)
working memory: holding items in memory (7+/−2) is achieved through interaction of the prefrontal and parietal cortex
firing properties related to more abstract features of a motor task I: dorsolateral prefrontal cortex neurons mark the beginning and ending of a behavioral episode
firing properties related to more abstract features of a motor task II: dorsolateral prefrontal cortex neurons track time intervals

TASK: monkey gets cues of different colors which indicate time interval to wait before releasing a key

 PREFRONTAL NEURONS: individual neurons respond for different cued time intervals – some build responses leading to key release time (below), some decrement responses following cue onset (above)
TASK: monkey gets sample image with 1-5 dots of varying size – delay – test images are given – one has the same number of dots, the other a different number (arrangement and size of dots varies) – monkey must select the one matching the sample image

PREFRONTAL NEURONS: exhibit delay activity specific to particular dot ‘counts’ irrespective of their size or arrangement
firing properties related to more abstract features of a motor task IV: dorsolateral prefrontal cortex neurons map action sequence categories

TASK: monkey observes a four-item sequence wherein three buttons (push, pull, turn) are lit in different combinations – monkey must remember the sequence and then perform it

PREFRONTAL NEURONS: have delay activity that corresponds to one of three ‘categories’ of action sequence (AABB, ABAB, AAAA)
the pattern of efferent projections from prefrontal cortex suggests three different pathways by which prefrontal cortex can enact ‘top-down’ influences on other regions of cerebral cortex (e.g., in some forms of attention)

1. direct projections
2. projections to neuromodulatory systems
3. projections to thalamus

basal forebrain ACh
locus coeruleus NE
substantia nigra/VTA DA
raphe 5-HT
an example: prefrontal ‘top-down’ influences on parietal cortex during an oculomotor delayed response task – inactivation of prefrontal cortex via cooling depresses ‘working memory’ responses of parietal cortex neurons and increases errors.

parietal neuron has delay-period activity specific to the N and NW targets.

delay-period activity for the same neuron is depressed when prefrontal cortex is inactivated.

error rate (percent saccades to wrong site) for each of 8 directions used increases when prefrontal cortex is inactivated.

Chafee and Goldman-Rakic, JNP, 2000
attention as a ‘selection’ process by which responses to stimuli are enhanced or suppressed – responses of neurons in IT cortex (part of the visual ‘what’ pathway) to their preferred stimuli are strongly modulated by attention

task: single visual cue (the target) is given followed by a delay – then two stimuli (one the target cue) are shown and the monkey saccades to the target cue –

premise: IT neurons have activity specific to particular objects during the cue phase – is their object-specific activity subject to the effects of attention?

when the pair of stimuli are presented, initially the neuron responds strongly, but this response is only transient if the preferred stimulus is not the target cue (dotted line) – the normal response of the neuron to the object has been suppressed relative to neurons whose preferred stimulus IS the target
the timing of attention – a role for prefrontal mapping of time intervals?

Task: Monkey is instructed to pay attention 1 of 4 regions of the visual field – when orientation of stimulus in that region changes, the monkey releases a bar.

Timing aspect: The probability that the orientation will change varies across time.

Activity of single neurons in visual cortex (area V4) responding to a visual stimulus fire more if their response field (RF) overlaps the region of the visual field that must be attended (‘attend in’ vs. ‘attend out’).

Subtracting the ‘attend out’ from the ‘attend in’ firing rate curve yields the ‘attention index’, which measures the difference in response to the stimulus due to attention.

The ‘attention index’ changes in accord with the probability that the stimulus will change orientation – that is, attention has a temporal component.
‘pop-out’ or ‘bottom-up’ attention versus ‘search’ or ‘top-down’ attention distinguishes the role of sensory cortex (parietal) versus prefrontal cortex.

Actual target (green line with NW orientation) is set within a group of three other potential targets – in pop-out setting, the other three differ in color AND orientation – in search setting, the other three differ in color OR orientation.

In pop-out setting, parietal cortex neurons (area LIP) are the first to have activity indicating target identification.

In search setting, prefrontal cortex neurons (area LPFC) are the first to have activity indicating target identification.

Buschman and Miller, Science, 2007