- Stability (posture)

Control of locomotion is affected by an integrated system and feedback & feedforward system

Intralimb coordination = in a single limb, the relative time of activation of different muscles, duration of activity and magnitude of activity needs to be coordinated
Interlimb coordination = precise coupling between different limbs

Stance and Swing

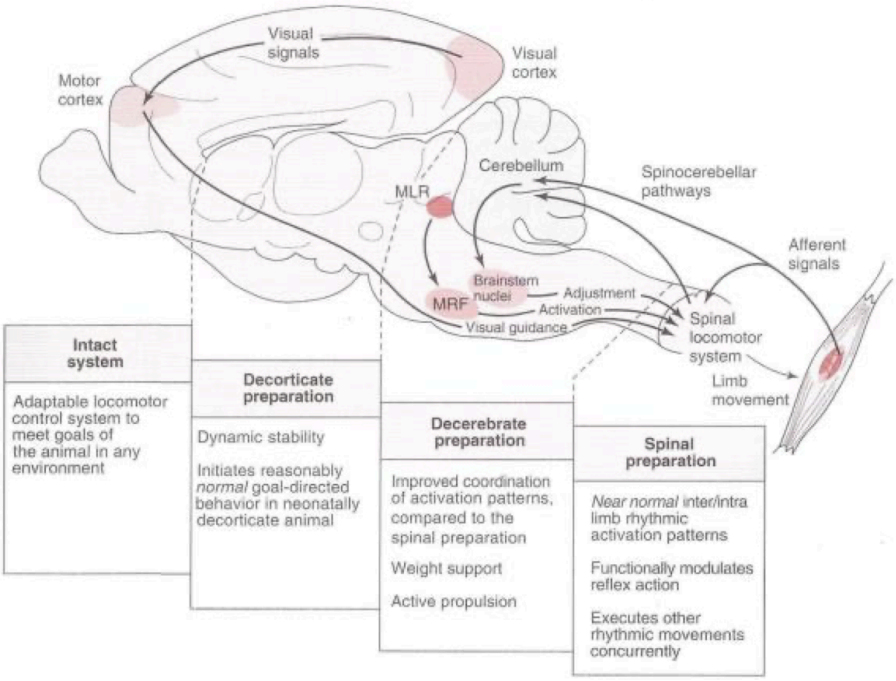
Swing phase → Foot is off grounadn being transferred forward

- F (flexion) and E1 (extension 1) periods
    - F: Flexion of knee, followed by activation of hip and ankle flexors
    - E1: Hip flexors contract, but knee and ankle flexors are arrested as the leg prepares for contact with support surface
        - Activity in most extensor muscles begins at this stage before the foot actually contacts the ground

Stance phase → Foot is in contact with ground and propelling body forward

- E2 and E3 periods
    - E2: Knee and ankle joints flex due to acceptance of body weight, extensor muscle lengthen and contract eccentrically at the same time
    - E3: Hip, knee and ankle all extend as the extensor muscles provide a propulsive force to move the body forward

Preparations



- Intact system
    - Can achieve goal directed movement
    - Cortex, brainstem and spinal cord structures are present and communicate
- Decorticate
    - No cortex, only brainstem and spinal cord structures
    - Some dynamic stability (due to brainstem)
    - Reasonable goal directed movement
- Decerebrate
    - No cortex and part of brain stem, spinal cord in tract
    - Some coordination of activation patterns
    - Weight support
    - Active propulsion
- Spinal preparation
    - Only spinal cord
    - Near normal inter/intra limb rhythmic activation patterns
    - Functionally modulates reflex action
- Fictive locomotion → examining locomotion with severed dorsal roots of spinal cord or paralysed muscles so there is no afferent input to the brain

Components in Locomotion

Locomotion requires a basic rhythm and patter generator → spinal cord

- Spinal cord has central pattern generators (CPG)

Feedback information from body and limbs are important for regulating aspects of the locomotor cycle (e.g. bending of body, stride length and force produced during propulsion) and ensures that

animals can react to unexpected perturbations in the environment. → proprioceptive and cutaneous

- Proprioceptive input is important for swing and stance phase timing, as well as amplitude of stepping
- Cutaneous input is important to allow stepping to adjust to unexpected obstacles

Feedforward information from supraspinal systems modifies activity according to the goals of the animal. → midbrain + brain stem, motor cortex, posterior parietal cortex

- Midbrain + Brain stem information is important for initiation of locomotion and regulating lomotor activity (e.g. speed, level of muscle activity and interlimb coupling)
    - **Mesenceohalic locomotor region (MLR)**: Cuneiform nucleus (CNF) + Pedunculopontine nucleus (PPN)
        - MLR projects to the medial reticular formation in the brain stem which then sends descending tracts to the spinal cord
    - **Subthalamic locomotor region**
- Motor cortex is important for visually guided movements
- Posterior parietal cortex is important for motor planning, especially when overcoming obstacles (it is important for the working memory of an obstacle)

Systems with no direct spinal connection also regulate locomotion → Cerebellum and Basal Ganglia

- Cerebellum regulates timing and intensity of descending signals → important for regulation of locomotion by comparison efferent copy of motor command with actual movement produced
- Basal ganglia is important for selecting different motor patterns

Spinal Cord and CPG

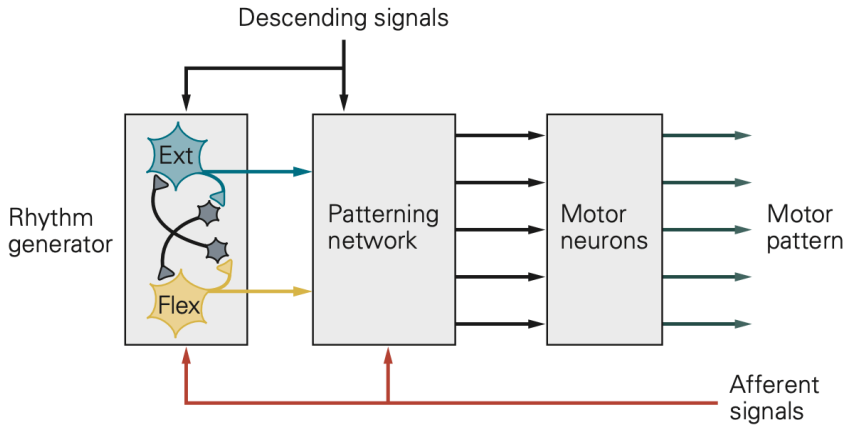
Central pattern generators (CPG) can genebrate both the rhythm and pattern, independent of sensory inputs.

- Experiment: Severed dorsal roots in cats
    - Well-organised locomotor pattern could be observed in decerebrate and spinal cats even after severiung the dorsal roots of the spinal and removing afferent feedback

There may be separate CPGs for each limb

- Experiment: Split belts
    - Animals can independently modify step cycle duration in each pair of limbs

Separate components of the CPG are responsible for generating rhythm and spatiotemporal pattern of muscle activation



- Rhythm generator → neuron controlling extensor and flexor motor neuron activation or suppression
    - Generate basic **rhythm** within limb
- Patterning network → a set of spinal interneurons that control the timing of different motor neuron activation
    - Generate spatiotemporal **pattern** in muscle action
    - Commissural interneurons (axons corss midline) involves in generating alternating rhythm
        - V0 commissural neurons important for left-right alternation at all speeds of locomotion
            - Inhibitory dorsal class of V0 controls alternating locomotion during walking
            - Excitatory ventral class of V0 neurons controls alternating locomotion during trot
        - V3 neurons important for synchrony in gaits such as bound and gallop

Afferent Inputs (Feedback)

Proprioceptive Inputs

Rate of locomotion in spinal and decerebrate cats are not affected. This observation suggests that sensory input from moving limbs signals different phases.

Stretch-sensitive muscle spindles (Hip) • Extension of hip joint leads to contractions in hip flexor muscles as flexor muscle spindles are activated ○ This extension/stretching of hip	Force-sensitive Golgi tendon organs (Ankles) • Activation of GTO in ankle extensor muscles prolongs stance phase and delays onset of swing phase

joint mimics the lengthending that occurs at the end of the stance phase (E3) ○ Therefore, extensor activities are inhibited and flexors are activated to prepare for swing phase ● Experiment (Mayer et al., 2018): ○ Proprioceptive feedback from muscle spindles important for modulating muscle activity amplitude during locomotion for mice. ○ Muscle spindle feedback to regulate the extensor activity increase at higher speeds ○ Mice with no muscle spindles couldn't achieve high speed in walking without ankle muscle spindles	○ It indicates that the ankle extensor has not been unloaded (force still exerted on ankle extensor), and the limb is not ready for the swing phase. ■ It needs to be in the stance phase for longer. ■ Ankle extensors important for stance ○ Action of 1b fibres on extensor motor neurons (which are homonymous/agonist muscles in this case) **reversed from inhibition to excitation** ■ During resting, stimualtion of 1b afferent fibres from ankle extensor muscles inhibits ankle extensor motor neurons through connection with inhibitory interneuon ■ During walking, 1b afferent send signals facilitated by descending signals to interneurons, opening a 1b excitatory pathway from GTO to extensor motor neurons, depressing inhibitory interneuron activity

Cutaneous Input

- Important for detecting obstacles and adjusting stepping movements to avoid them
- Experiement: Cat paw stimulation
  - Mild mechanical stimulus applied to dorsal part of cat paw during swing phase → excitation of flextor motor neurons and inhibito of extensor motor neurons
  - Rapid flexion of paw away from stimulus and elevation of leg
  - However, corrective flexion movements only produced when paw stimulated during swing phase
  - Identical stimulus applied during stance phase → excitation of extensor muscles that reinforces ongoing extensor activity

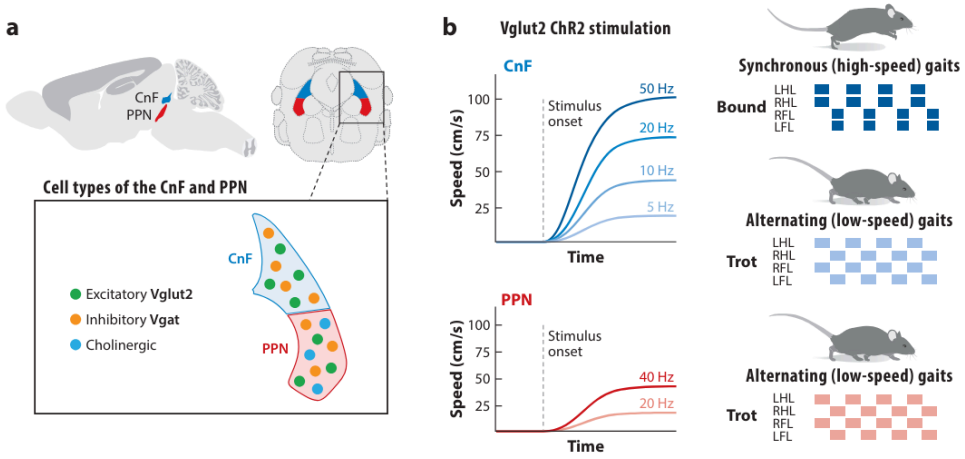
        - If flexion reflex were produced during stance phase, animal might collapse because weight is being supported on that limb
            - Phase-dependent reflex reversal ⇒ same stimulus can excite 1 group fo motor neurons during 1 phase of locomotion while activating antagonist motor neurons in another phase

Midbrain and Brain Stem

Midbrain: MLR & SLR

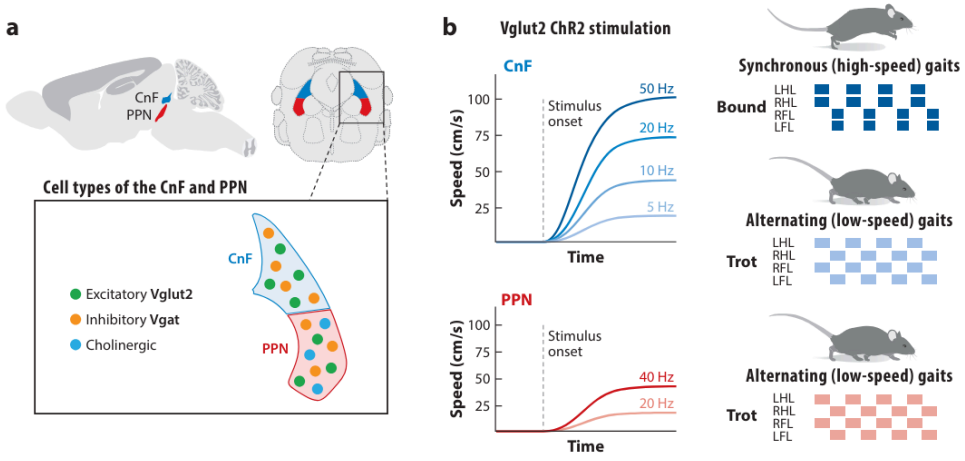
Mesencephalic locomotor region (MLR) is located in the midbrain ventral to the inferior collicus, and comprises of two nuclei:

- Cuneiform nucleus (CNF)
    - Glutamatergic projections
    - Local GABAergic interneurons
    - Important for high-speed locomotion speed (e.g. gallop and bound)



    - Experiment (Caggianno et al., 2018)
        - Stimulating glutamergic neurons expressing excitatory Vglut2 from CNF initiate movements
        - Initiate high speed locomotion with greater stimulus (e.g. 50Hz) while weaker stimulus resulted in slower movements like walking (e.g. 10Hz)
            - Influences ongoing movement speed
    - Receive inputs from:
        - Structures involved in escape response
- Pedunculopontine Nucleus (PPN)
    - Glutamatergic and cholinergic projections
        - Cholingergic projections may have very little effects on locomotion in mammals, although some studies have demonstrate that it may decrease slight the speed of locomotion

- Local GABAergic interneurons
- Only involved in low speed gaits (e.g. walking)



-
- Experiment (Caggiano et al., 2018)
    - Stimulating glutamergic neurons expressing excitatory Vglut2 from PPN only initiate slow speed movements regardless of increasing stimulus strength
- **Locomotion promoting effect strictly limited to the caudal region of the PPN, rostral region of PPN controls whole-body motor arrest**
- Receive strong inputs from:
    - Basal ganglia (Substantia nigra pars reticulata & Globus pallidus pars interna)
    - Subthalamic nucleus
    - Sensorimotor and fontal cortex
    - Many nuclei in midbrin and brain stem

MLR is initiates locomotion (sends start signal)
Both nuclei are important in speed control and gait selection of locomotion.
Select context-dependent locomotor behaviour.

Subthalamic locomotor region (SLR):

- Includes nuclei in dorsal and lateral hypothalamus which have a role in regulating feeding
- Neurons bypass PPN and CNF and project directly to reticular formation in brain stem –. Parallel pathway for initiating locomotion, possibly drive by need to find food

Brain Stem

Relaying MLR Signals

Excitatory signals from CNF and PPN are sent to the neurons in the reticular formation in brain stem before relayed to the spinal cord.
MLR → medial medullary reticular formation (MRF) in brain stem → spinal cord
The MRF send descending tracts in the ventrolateral funiculus (VLF)

2 transmitter-defined pathways are involved: glutamatergic and serotonergic

- Glutamatergic
    - Origins in brain stem reticular formation, forming parallel descending pathways
    - Project directly or indirectly via a chain of propriospinal glutamatergic interneurons to locomotor neurons in spinal cord
- Serotonergic locomotor pathway
    - Involvement of serotonergic neurons in caudal brain stem in mice

Episodic nature of locomotion indicates that initiating signals is complemented by stop command

- V2a neurons in reticular formation mediate immediate arrest of ongoing locomotor actvity

Brain Stem Nuclei

Regulation of posture (including postural support, control of balance, regulation of interlimb coordination, modification of muscle tonus (resting tension) required to adapt to slopes or during turning)

- **Lateral vestibular nucleus** (LVN)
    - Vestibulospinal tract
- **Pontomedullary reticular formation** (PMRF)
    - Reticulospinal tract (RST)

Lesions in LVN and PMRF or their descending axons lead to loss of weight support and control of equilibrium, as well as large changes in interlimb coordination

Activity of VST and RST with rubrospinal tract (originating from red nucleus) modifies level of muscle tonus during each step.

- Weak electrical stimulation of VST, RST or rubrospinal tract produce phase-dependent modulation of locomotor activity
    - Brief activation → transient changes in amplitude of muscle bursts, but rarely produced any changes in timing of step cycle
- Activation of nucleus
    - Stimulation of LVN enhances response in ipsilateral extensor muscles during stance phase
    - Stimulation of red nucleus causes transient increases in contralateral flexor muscle activity during swing phase
    - Stimulation of PMRF causes modifications to activities in flexor muscles during swing phase and in extensor muscles during stance phase
        - Flexor muscle activity generally facilitated by PMRF stimulation

- Extensor muscle activity may be facilitated or suppressed depending on exact site stimulated
- PMRF contributes to compensatory change sin posture that occur as a consequence of pertubations

Motor Cortex

Motor cortex is important for visually guided locomotion.
Lesions of motor cortex severely impair precision locomotion, which requires a high degree of visuomotor coordination (e..g stepping over objets)

Experiment:

- Considerable modulation of activity of numerous neurons in motor cortex when intact cats step over obstacles on moving treadmill

Corticospinal tracts (CST) projection directly to spinal cord regulate the activity of spinal interneurons, adapting timing and magnitude of motor activity to a specific locomotor task.

Brief electrical stimulation applied to either the motor cortex or CST lead to transient response in contralateral limb in a phase-dependent manner.

Prolonged electrical stimulation lead to reset of locomotor rhythm as the step cycle is interrupted and a new step cycle is initiated → suggest that CSt has privileged access to rhythm generator of CPG.

Posterior Parietal Cortex

Posterior parietal cortex (PPC) important for planning gait modifications

Experiment:

- Lesions in PPC leads to walking cats to misplace paws as they approach obstacle and increase probability that 1 or more legs contact the obstacle as they step over it
- PPC display increase in activity in advance of the step over the obstacle.
    - PPC discharge similarly regardless of which leg is first to step over obstacle.

Visual information (e.g. size and location of obstacle) is stored in working memory (short term memory) to ensure that gait modifications in the hindlinmb are coordinated with those of the forelimb because the obstacle is no longer in view by the time the hindlimbs have to step over it.

PPC is important for this working memory.

Experiment:

- Bilateral lesions or cooling of the medial PPC led to abolishment of memory of obstacle.
- Activity of PPC is elevated during a step over an obstacle and throughout the time the animal straddles (stands over) the obstacle

Cerebellum

Cerebellum is important for the regulation of locomotion.
Its major function is to correct movements based on a comparison of the motor signals sent to the spinal cord and feedback from actual movement.

- Information about the movement comes from ascending spinocerebellar pathways
    - Signals of mechanical state (proprioceptive inputs) of hind legs via dorsal SCT
    - State of spinal locomotor network (by interneurons in the CPG) via ventral SCT

Motor command (central efference copy) + movement (afference copy via dorsal SCT) + state of spinal network (spinal efference copy via ventral SCT) are integrated within the cerebellum

- Output is expressed as changes in pattern of rhythmical discharge of Purkinje cells, and consequently changes in activity of neurons in deep cerebellar nuclei
- These signals are then sent to motor cortex and other brain stem nuclei to modulate descending signals

Basal ganglia

Basal ganglia is important for the selection of different motor patterns

Parkinson's:

- Disruptions in normal functioning of basal ganglia due to degradation of dopaminergic inputs from substantia nigra
- Symptoms:
    - Slow, shuffling gait
    - Problems with balance during locomotion and anticipatory postural adjustments that occur at initiation of gait pattern

Basal ganglia contribute to initiation, reuglatio and modification of gait patterns.

Basal ganglia influence brain stem activity through their projections to the PPN.

- PPN receives:
    - Inhibitory inputs (from GABAergic neurons in the substantia nigra pars reticulata and globus pallidus pars interna)
    - Excitatory inputs (from glutamatergic neurons in the subthalamic nucleus).
- Increase in excitatory inputs and decrease in inhibitory inputs promote activity in PPN and favour exploratory locomotion

Basal ganglia influence cortical activity by means of its connections via the thalamus to different parts of the frontal cortex (e..g SMA) → modulatory effect on visually guided locomotion

Human Locomotion

Some patients with spinal cord injuries parallel spinal cats

- For example:
    - Patients with nearly complete transection of spinal cord show uncontrollable movements of legs when hips are extended
- CPGs are present in humans and share functional similarities with CPGS found in other vertebrates

Infants make rhythmic stepping movements immediately after birth if held upright and moved over a horizontal surface

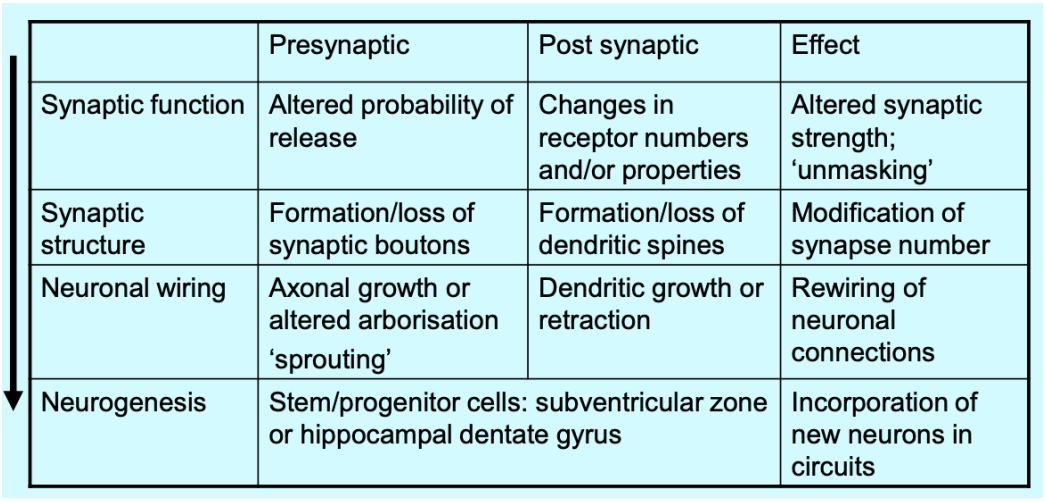
- Basic neuronal circuits for locomotion are innate and present at birthday despite descending control systems not being well developed
- Stepping can also occur in infants who lack cerebral hemispheres (anecephaly) –. Circuits must be located at or below brain stem
- Automatic stepping is transformed into functional walking later in life as basic circuits are brought under supraspinal control
    - Mature pattern of complex movements can be generated

Stroke involving motor cortex or damage to CST leads to deficits in locomotion

- Deficits in humans are much stronger when CST or motor cortex are damaged
    - Motor cortex in humans plays a more important role in locomotion than in other mammals

Synaptic Plasticity

- **Plasticity is synaptic modulation**
- Synaptic modulation underlies learning and memory processes
- Modulation of synapse can occur at:
    - Presynaptic
        - Modification of the amount of NT release
    - Synaptic cleft
        - Modify the reuptake of the transmitter
    - Postsynaptic
        - Greater sensitivity to transmitter, modify receptor/ion channel
- Hebbian principle: “neurons that fire together, wire together”
    - Neurons have to have causal links and become associated together

    - When axon of cell A is near enough to excite cell B or repeatedly takes part in firing it, some growth process of metabolic change takes place such that A's efficiency in stimulating B increase
- Cerebral plasticity is the dynamic potential of the brain to reorganise itself during otogeny, learning or following damage
    - Change in neuron structure or function
- Plasticity is important for:
    - Elaboration of new circuits induced by learning, and maintenance of neural networks in adults
    - After damage to peripheral or CNS, functional reshaping underlying clinical recovery
- Features:
    - Activity-dependent (physical or mental)
        - Synaptic plasticity specifically refers to activity-dependent modification of strength of efficacy of transmission at pre-existing synapses
    - Continues throughout life
    - Basis of learning and memory
    - Can help or hinder
        - Advantageous or maladaptive
    - Continuous
    - Basis in synapse
    - **Associated with altered cortical topographical maps**
    - Can be short or long term
    - Occurs in response or lesions
    - Greatest during development and declines with age
- 

	Presynaptic	Post synaptic	Effect
Synaptic function	Altered probability of release	Changes in receptor numbers and/or properties	Altered synaptic strength; 'unmasking'
Synaptic structure	Formation/loss of synaptic boutons	Formation/loss of dendritic spines	Modification of synapse number
Neuronal wiring	Axonal growth or altered arborisation 'sprouting'	Dendritic growth or retraction	Rewiring of neuronal connections
Neurogenesis	Stem/progenitor cells: subventricular zone or hippocampal dentate gyrus		Incorporation of new neurons in circuits

    - Early changes are functional
    - Persisting plasticity lead to changes in structure etc etc
    - Neurogenesis: New neurons can be developed and incorporated into circuits
- Mechanisms:
    - Fast (msecs, minutes, hours)
        - **Functional changes** → short term changes
        - Functional modulation of existing synapses
        - Unmasking of preexisting cortical connections
        - Strengthening or weakening of pre-existing synaptic connections

        - Examples:
            - Short-term potentiation
            - Long term-potentiations
            - Long term depression
        - Repeated stimulation or paired associative stimuli
    - Slow (days to weeks)
        - **Structural Changes**
        - Sprouting and formation of new synapses
            - Increased number of dendritic spines
            - Dendritic elongation
            - Axonal branches
            - Receptor density/transmitters
        - Recruitment of other areas

Functional Changes

LTP and LTD occur due to activity (**activity dependent plasticity**)
First described in hippocampus
Various neurotransmitters are modulated (e.g. GABA decrease, glutamate upregulated)
Synapses are potentiated or depressed (LTD/LTP) or unmasked

Functional plasticity is the brain's ability to reorganise its functions by strengthening/weakening existing synapses, and unmasking of new connections.

Short Term Plasticity

Triggered by short bursts of activity causing a transient accumulation of calcium in presynaptic nerve terminals → changes in probability of neurotransmitter release

Important for influencing the information processing function of synapses, filtering information.

Paired-pulse Plasticity

When 2 stimuli are delivered in a short interval, the response to the second stimulus can be enhanced or depressed relative to the response to the first stimulus

Whether a synapse exhibits paired-pulse facilitation or depression depends on recent histroy of activiation of synapse

- Synapses tha begin with a high probability of release tend to depress response to second pulse (Dobrunz and Stevens., 1997)
    - Manipulations of presynaptic release probabilities thus can modulate whether a synapse will experience paired-pulse facilitation or depression (e.g. lower release

proability by activating presynaptic inhibitory autoreceptors cause an increase in magnitude of paired pulse facilitation)

Potentiation:

- Occur at shorter interstimulus intervals (less than 20ms)
- Residual calcium left over from invasion of first AP contributes to additional release during second stimulation
    - More complex mechanism (De Camilli et al., 1990)
        - Mice with presynaptic phosphoprotein, synapsin, knocked out = abnormal short term plasticity

Depression:

- Occur at longer interstimulus intervals (20-500ms)
- Transient depletion of release-ready pool of NT vesicles in presynaptic terminal

Long Term Plasticity

Associative memories are formed in the brain by a process of synaptic modification that strengthens connections when presynaptic activity correlates with postsynaptic firing (potentiation)

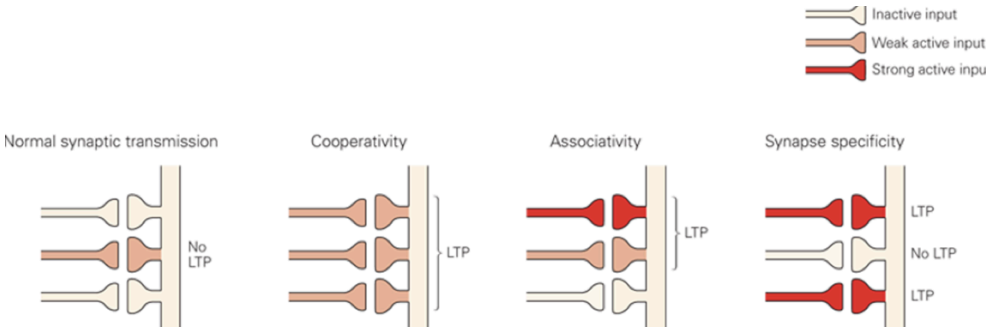
Activity-dependent, long-lasting increase in synaptic efficacy (hours to years)

Excitatory synapses are bidirectionally modifiable by different patterns of activity

LTP

Characteristics of LTP

Input specificity, cooperativity and associativity all encoded by NMDA

- 

    - Cooperativity (3 weak inputs)
        - Weak synapses cooperate to overcome threshold for releasing Mg^{2+} block
    - Associativity (1 strong input with 1 weak input, coincidental, linked together)
        - Weak synapses associate with strong synapse to overcome threshold for releasing Mg^{2+} block
    - Input specificity
        - LTP only elicited at activated synapses and not adjacent, inactive synapses on the same postsyanptic cell

        - This feature increases storage capacity of individual neurons since different synapses on the same cell can be involved in separate circuits encoding different info

- Short period of high-frequency stimulation → EPSP amplitude enhanced and persisted for several horus (Bliss & Lomo., 1973)
    - Long term potentiation are triggered
    - 4 phases of LTP:
        - Short term potentiation (STP)
            - Lasts up to one-hour
            - No protein kinase needed
            - Temporary process
            - Can have reorganised of cortical network and enhancement of cortical excitability
        - **Early LTP**
            - **Requires protein phosphorylation**
        - LTP2
            - Protein synthesis
        - LTP3
            - Gene transcription
- Basis of LTP → repeated stimulation → intracellular events leading to functional changes (dependent on calcium)

Example in CA1 region of hippocampus → NMDA dependent

- Receptors
    - NMDA receptors = high threshold receptor, blocked by Mg^+ can only be removed by high depolarisation, contributes little to EPSP during basal synaptic activity, allows Ca^{2+} and Na^+
    - AMPA receptors = permeable to monovalent cations (Na^+ and K^+), provide most of the inward current which generates EPSP during basal synaptic activity
    - AMPA receptors often coexist on postsynaptic membranes with NMDA receptors
- Mechanism of early LTP
    - AMPA receptors activate
    - Strong enough depolarisation generated
    - NMDA receptors without magnesium block
    - Calcium influx
        - Ca^{2+} levels exceed a critical threshold value
    - Calmodulin activated
    - Calmodulin-dependent protein kinase II (CaMKII) activated → increase AMPA channel conductance by phosphorylating it
    - PKA activated → more AMPA receptors inserted into the postsynaptic membrane (exocytosis)
    - Also more insertion of NMDA receptors
- Experiment
    - Normally achieved through applying high freq tetanic stimulation to the synapse or by using pairing protocol

LTD

- Prolonged low-frequency stimulation induces depression (~5Hz)
- Can be induced by correctly timing the activation of presynaptic axons and postsynaptic neurons (aka STDP)
- Mechanism
    - LTD requires modest increase in Ca^{2+} (Malenka RC 1994)
        - Modest increase optimal for LTD
          Large increase optimal for LTP (large depolarisation ⇒ more NMDAR activated ⇒ good for LTP)
    - Activation of Ca^{2+} dependent protein phosphatase cascade which involves a protein named protein phosphatase 1 (PP1)
        - Loading CA1 pyramidal cells with PP1 enhances LTD (Morishita et al., 2001)
    - Dephosphorylation of postsynaptic PKA substrates
    - AMPA receptors are removed from membrane (endocytosis back into neuron)

Spike timing dependent

Spike timing dependent plasticity is the observation that precise timing of spikes significantly affects sign and magnitude of synaptic plasticity.
Often used to induce LTP and LTD in experiments.

Presynaptic AP precedes postsynaptic AP = LTP

- Synapses increase in strength if presynaptic spikes repeatedly occur before postsynaptic spikes within around 10ms or less

Postsynaptic AP precedes presynaptic AP = LTD

LTP and Unmasking

Silent synapses prevalent during development

Presynaptically silent = AP doesn't trigger release of Ca^{2+} and NT release
Postsynaptically silent = NT is released but there is uptake postsynaptically

- Contain only NMDARs with few or no AMPARs, so at normal resting memrabne potentials, these synapses exhibit no postsynaptic responses to synaptically released glutamate
- Unsilenced via incorporating AMPARs
    - LTP induction can unmask silent synapses
    - Unmasking postsynaptic membranes: Channels inserted into postsynaptic membrane

Unmasking is very fast (may underlie maladaptive change)