

Unmasking can underlie somatosensory map reorganisation → Lateral inhibition is controlled by GABAergic inhibition

- Functional maps are maintained by the inhibitory system
 - Excitability of horizontal connections involved in map-modelling controlled by GABAergic inhibitory system
 - Inhibitory system regulated by sensory information about the state of peripheral motor apparatus
- Experiment (Jacobs and Donoghue., 1991)
 - Motor nerve innervating a muscle (mystacial vibrissa) is transected
 - M1 reorganisation
 - Region of motor cortex modifies its output organisation so that 1 set of cortical neurons influences a new set of muscles
 - Rapid → rather than growing new connections, existing synaptic connections alter their effectiveness
 - **Relief of inhibition can facilitate the strengthening of synaptic efficacy of neighbouring synapse** to the region which the transected motor neuron originates in → lateral inhibition by GABA
 - GABA projections to nearby pyramidal neurons, and suppress effectiveness of excitatory drive from surrounding representations
 - Modulations to GABA release = unmasking of connections → reorganisation of cortical map

When reorganisation of somatosensory map (due to peripheral sensory deprivation) is acute = unmasking of connections. The injured cutaneous receptive field cortical areas becomes responsive to stimuli from adjacent area

Homeostatic Plasticity

Stabilise neural circuits → strength of all synapses on a cell are adjusted in response to prolonged changes in activity

- Balance changes in neural activity to maintain homeostasis over a wide range of temporal and spatial scales
- Prolonged decrease in overall activity cause net scaling up of total synaptic strengths; prolonged increase in overall activity causes net scaling down of total synaptic strengths

Slower timescale

Important during the development of neural circuits

Can be functional or structural

- Functional:
 - Synaptic scaling
 - Neurons detect changes in their own firing rate through Ca^{2+} dependent sensor which regulate receptor trafficking
 - Increase/decrease number of glutamate receptors at synaptic sites

- Structural:
 - Removal of dendrites / growth of dendrites to balance out activity

Structural Changes

Structural plasticity is the physical changes the brain undergoes following persistent functional plasticity, thus this will involve the sprouting of new axons, formation of new synapses etc.

- If long term plasticity persists then it may lead to structural changes
 - Activity dependent trafficking of AMPARs into and out of synapses during LTP and LTD is the first step into the growth or shrinkage of synapses, and thus the first step to maintain a certain synaptic strength (e.g. potentiation or depression)
- Axons can sprout, change trajectory or may be eliminated
 - More dendrites = more synapses = potentiation
- Altered cortical representational maps

Plasticity and Lesion

Optimising redundant / inactive areas

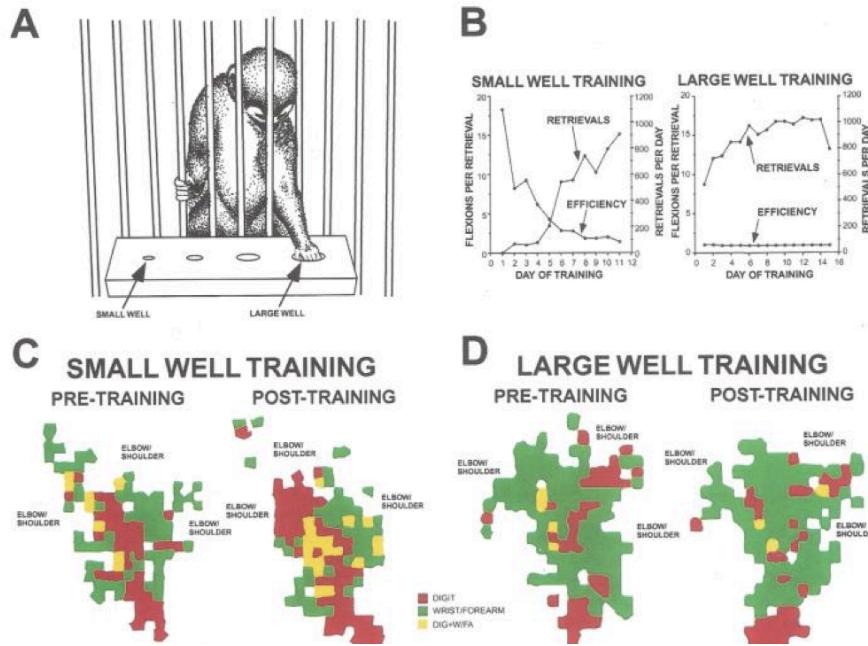
- Multiple areas of representations → some areas may take over
 - Post lesion → other areas take over the control for the lesioned area
 - Neuronal activity reduces in lesion zone → stronger activity from adjacent areas to lesion zone

Adaptations of visual cortex to retinal lesion:

- Neuronal activity in lesion zone decreases
- Functional changes: Strengthening of pre-existing inputs from cells in adjacent areas (LTP)
- Structural changes: Axonal sprouting into lesion zone
 - BDNF is increased (promotes dendritic growth)
 - Inhibitory neurons retract axonal arbor
 - Levels of GABA decrease
 - Increase in excitation
 - Disinhibition in peri-lesion zone
 - This way they can take over functions of lesion area
 - Increase in excitatory axonal sprouting in peri-lesion zone
- Overtime new circuitry stabilizes

Examples

- Altered afferent input can change sensory cortical representations
 - Insert fine electrodes to stimulate cortical areas of monkey
 - Response to cutaneous stimulation recorded
 - Rotating disk gave stimulation (cutaneous) to 2nd and 3rd digits
 - Stimulation expanded map representation → 2nd and 3rd representational map expanded
 - Repeated stimulation led to plasticity
- Structural abnormalities causing altered afferent feedback
 - Experimental syndactyly (2 fingers fused as one) in monkeys
 - Overlap in the map in cortical areas for fused digits
 - Shared representation
- Altered behavioural experience can lead to altered motor cortical representations
 - Monkey trained to pick food from different sized wells
 - Large well training: efficiency did not increase
 - Small well training: efficiency increased, rate of retrievals increased
 - Cortical map reorganised
 - Particularly digital and wrist cortical maps expanded
 - Activities need to be the right type of challenging to induce plasticity



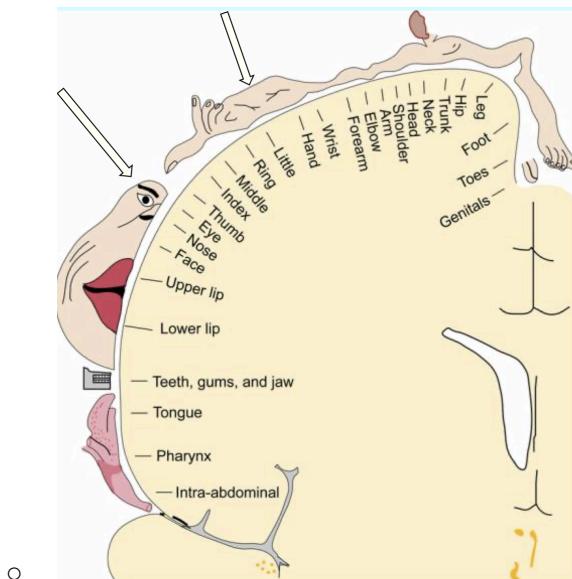
- Age / developmentally related neuroplasticity and learning
 - Increase
 - Musical training when very young improves cortical connections
 - Greater excitability when trained younger than older
 - Activity dependent plasticity
 - Training in sensitive period induced long lasting changes in excitability of cortex

- Decrease
 - Pruning of synapses as a child grows
- Environment enrichment contributes to synaptic plasticity
 - Increased dendritic spines (synaptogenesis) in CA1 after enrichment in mice (recovery from NMDAR knock-out in CA1 which caused impaired non-spatial memory that is dependent on hippocampus)
 - LTP amplitude enhanced in dentate gyrus of mice
 - Song birds exposed to enriched environment leads to an increased expression of NGF, BDNF and GDNF which promote neurogenesis
- Neurogenesis
 - Neurogenesis potential declines with aging
 - Implicated in Alzheimer's Disease
 - Spine remodeling and formation of new synapses are activity-dependent processes that provide a basis for memory formation
 - A loss or alteration of these structures has been described in patients with neurodegenerative disorders

Cortical Plasticity

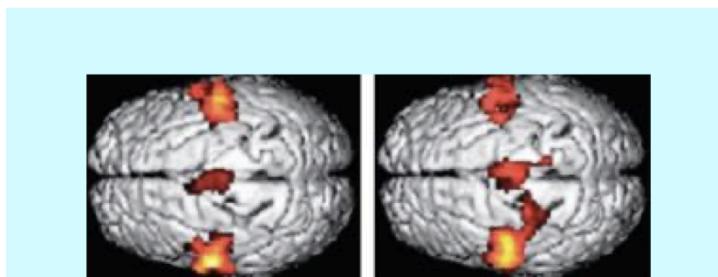
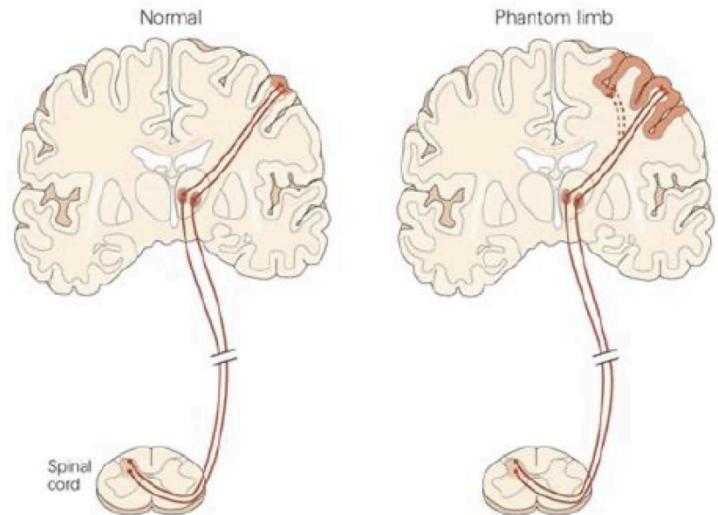
Phantom Limb

- Phantom limb sensation → sensation from an absent limb following amputation
 - Pain
 - Occur in first stages after amputation
- **Reorganisation of sensorimotor cortices associated with amputation**
 - Somatotopic map



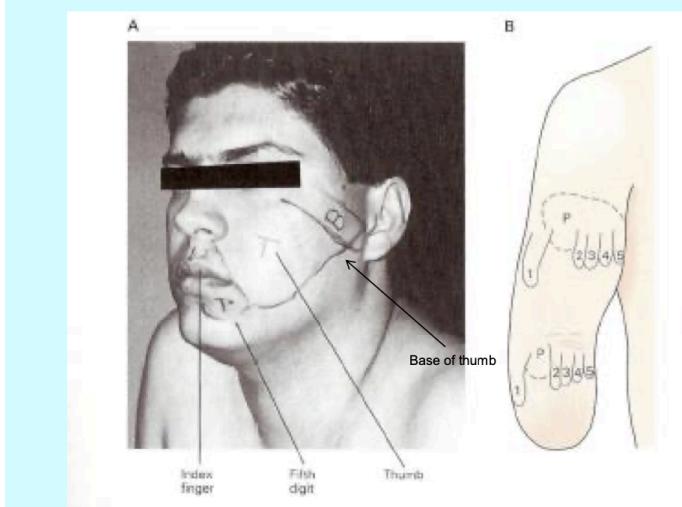
- Denervation (loss of nerve supply) leads to other neurons invading the area

- Sensory afferents branch and become stronger in their connectivity in neighbouring areas which was lost (e.g. stronger connections to facial area after loss of hand)

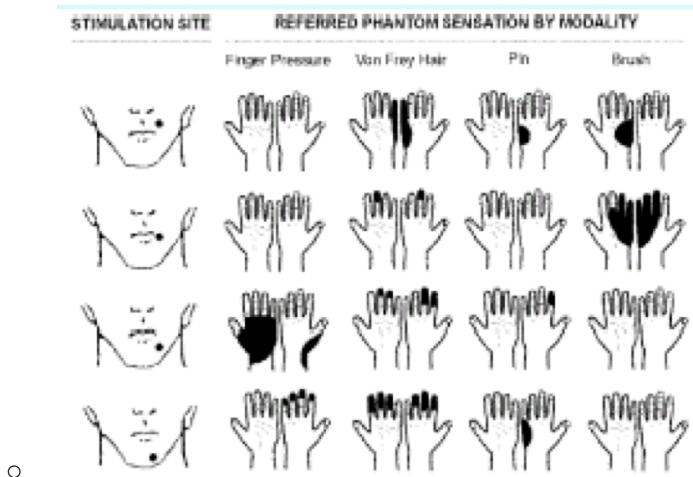


- Cortical reorganisation following limb amputation

Ramachandran, 1993 (MEG study)



- Can feel hand area after being touched in the face
- Maladaptive cortical plasticity following limb amputations
 - Mostly likely due to unmasking / disinhibition
 - Rapid changes can occur within 24 hours
 - Changes are modality specific (specific to type of sensation, for example, what type of touch, pin or brush etc)

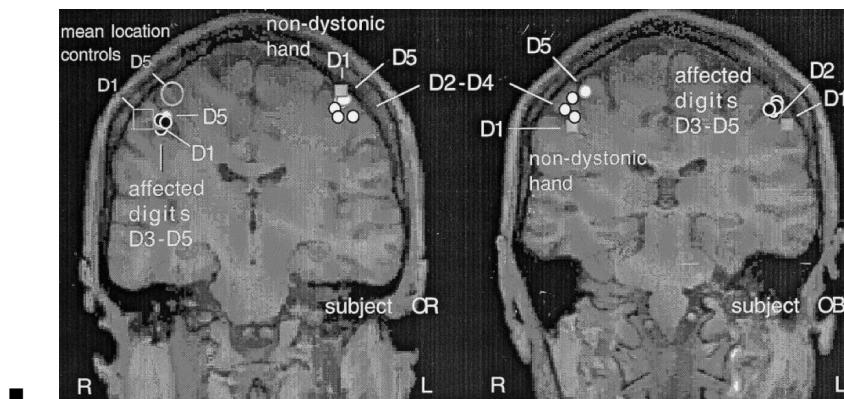


- The person is touched in a specific area of the face with touches with different modalities (e.g. pin, brush) and different areas of the hand was felt
- Treatment of phantom pain → Mirror therapy
 - Procedure
 - Phantom limb patient
 - Put complete limb into mirror box and move with intact limb
 - Altered sensation of pain
 - Patients felt they were moving their phantom limb
 - Doesn't work with everyone
 - Experiment (Foell et al., 2013)
 - Daily mirror training over 4 weeks with patients with unilateral arm amputation
 - Participants performed hand and lip movement during a fMRI measurement before and after mirror training
 - Lip movements of those with phantom limb pain activates lip and hand/arm area
 - Location of neural activity in primary somatosensory cortex was used to assess brain changes related to treatment
 - Treatment caused reduced phantom limb pain (average decrease of 27%)
 - fMRI data revealed that mirror training caused a reduction in the dysfunctional cortical reorganisation in S1 (primary somatosensory cortex)
 - Post training decreased shift of cortical area representing lip

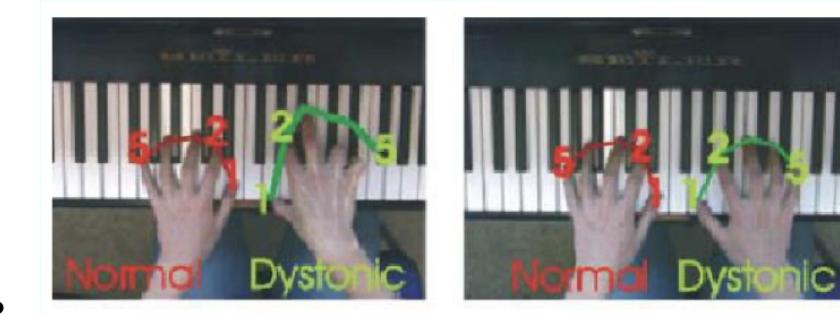
Focal Dystonia

- Maladaptive plasticity → changes in sensory cortex and associated with repetitive strain injury and dystonia
- Repetitive Strain injury
 - Often reported by people who repetitively perform fine motor skills such as writing, keyboard skills and stringed instrument
 - Experiment (Byl et al., 1996)
 - Moneky trained to develop repetitive strain injury

- Behavioural task that requires them to maintain an attended grasp on a hand grip that repetitively and rapidly opened and closed over short distances
- Completed 1000 - 3000 movement events per day
- Researchers mapped representations of the hand within primary somatosensory cortical zone
- Hand representation cortical areas degraded in monkeys
 - De-differentiation of cortical representations of the skin of the hand
 - Selectivity of cortical neuronal responses is indicated by size of cutaneous receptive fields
 - These fields were larger after strain injury → loss of selectivity
 - Neurons had multiple component receptive fields with subfields on more than 1 digit
 - Breakdown of normally sharply segregated, independent representations of fingers areas
- Focal Dystonia
 - Neurological disorder causing involuntary muscle movements or contractions in just 1 part of the body
 - Patients complain of cramps
 - Associated with agonist and antagonist co-contraction
 - Use-dependent alteration of the sensory cortex may be involved in etiology of focal dystonia
 - Problems with muscle sequencing and involuntary movements during task
 - Experiment (Elberr et al., 1998)



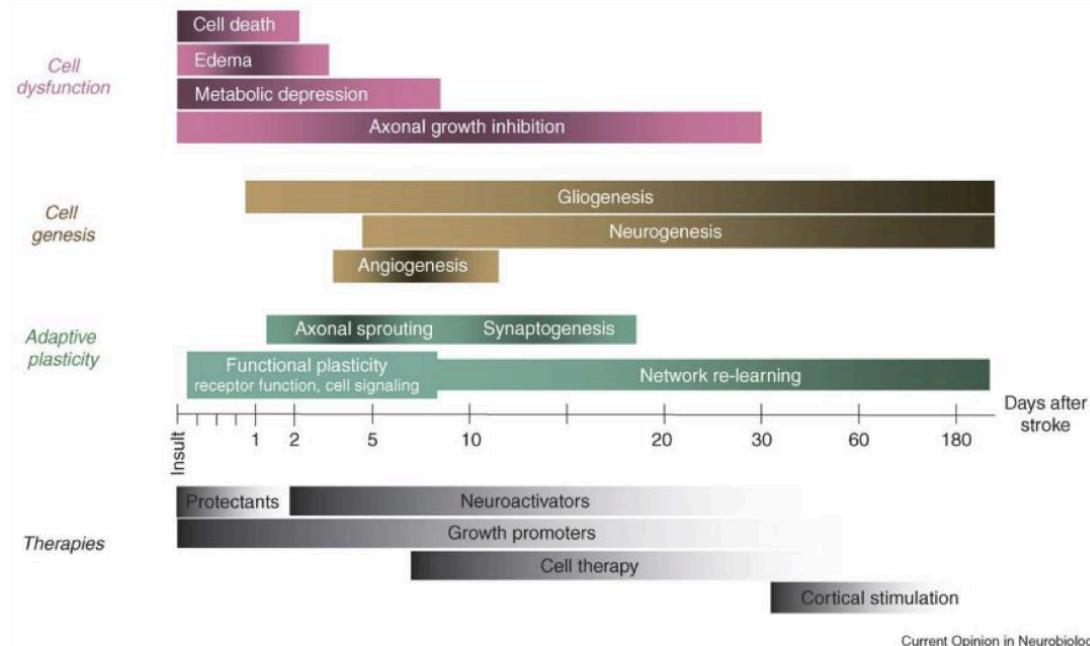
- Patient digits 1 and digit 5 overlapped
- Treatment: Splinted rest of fingers, affected digits forced to be used



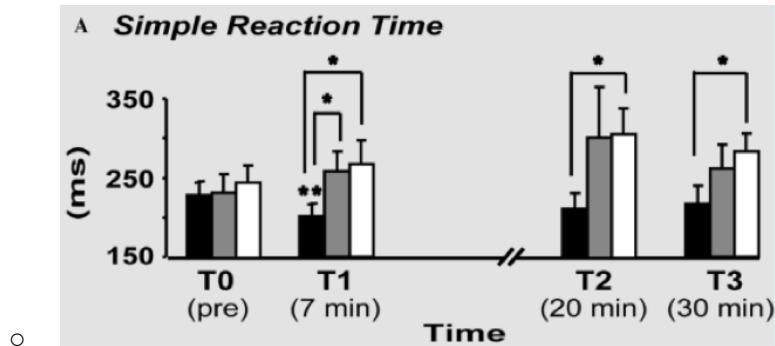
- Changes in cortical maps following training of affected fingers to produce discrete representations

Stroke

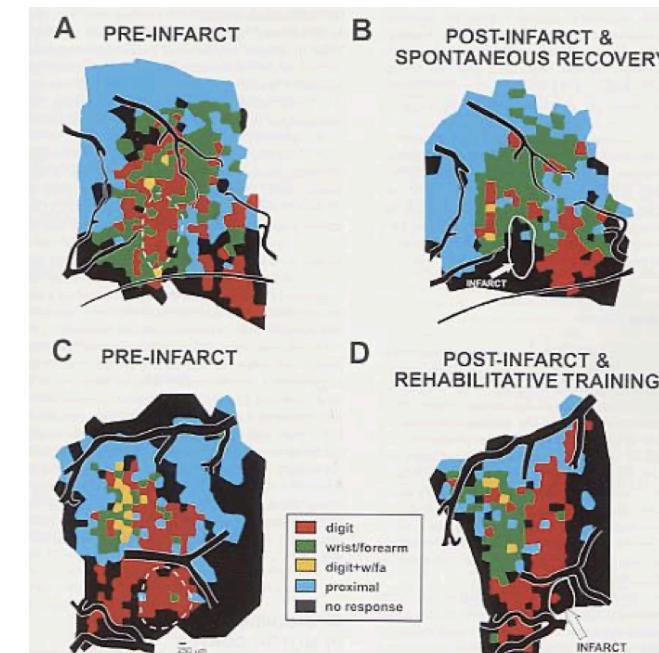
- Stroke results from a CNS lesion caused by a clot (resulting in ischaemia) or by hemorrhage in brain circulation
- Pathophysiology
 - Excitotoxicity → due to release of excessive glutamate
 - Cell death signalling pathways activates
 - Neuroinflammation and blood-brain-barrier break down
 - Oxidative stress which is characterised by
- Lesions usually affect motor areas, but can also affect sensory areas and subcortical & brain stem areas
 - Loss of sensory feedback makes learning difficult
 - Typically affects corticospinal tracts
- Outcomes depend on area of damage
 - Unilateral, affects only one side of the body with loss of motor skills on the opposite side
 - Particularly fine motor skills (e.g. precision grip, swallowing, speech)
- **Infarcted area has a central area of dead neuronal tissues surrounded by areas where neuronal death is less severe (penumbra) as well as distant functionally connected sites which show prolonged but reversible depression of activity (diachisis)**
- Altered motor behavior due to paralysis and / or spasticity on opposite of body
 - Learned non-use
- Recovery / Rehabilitation = motor re-learning = manipulates neuroplasticity
 - Experience-dependent (activity-dependent) plasticity / homeostatic plasticity



- Mechanisms of recovery
 - Reversal of diaschisis, which is the functional deactivation of remote structurally normal areas
 - Resolution of oedema
 - Peri-infarct re-organisation
 - Reorganisation of M1, premotor and supplementary areas
 - Neuroplasticity: Dendritic sprouting, new synapse formation, LTP, unmasking (Both functional and structural)
 - Activity in contralesional cortex
 - May assist or inhibit recovery
 - Interhemispheric interactions
 - Abnormally high interhemispheric inhibition can be dampened down using brain stimulation
- Recovery will depend on extent and site of lesion
- Interventions to Promote Neuroplasticity
 - Salvage therapy (less than 24 hours past stroke)
 - Non-invasive brain stimulation (e.g. TMS)
 - Attempt to enhance neuroplasticity (**functional plasticity**)
 - Repetitive TMS stimulation (**rTMS**) involves delivering several pulses of TMS to the cortex in a short period
 - Continuous theta burst stimulation cTBS = LTD
 - Intermittent theta burst stimulation iTBS = LTP
 - Delivering TMS pulses to lesioned cortex can improve its connections
 - Increase in CST transmission and motor function
 - Experiment (Talelli et al., 2009)
 - Short intervention
 - Positive effect was found for intermittent bursts stimulating the lesioned cortex only

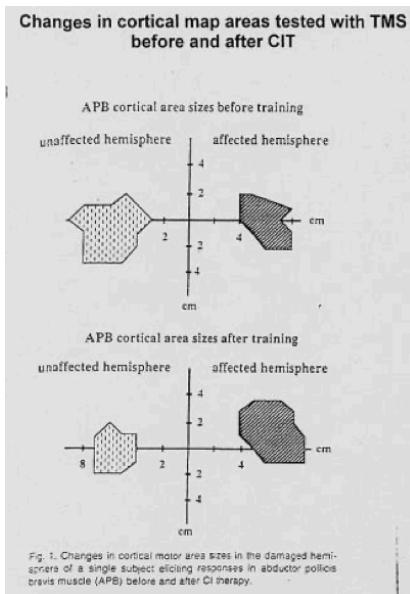


- ■ Reaction times decreased
- TMS very lab based intervention, effects not very clear
- Transcranial direct current stimulation (**tDCS**) can also work
- Experiment (Hummel et al., 2005)
 - tDCS (transcranial direct current stimulation) improved hand function as Jebsen-Taylor Hand Function Test time decreased (e.g. less time for turning over cards, picking up small objects etc)
 - tDCS increased cortical excitability
- Forced use of affected limb (physical therapy)
 - **Structural plasticity**
 - Reorganisation of cortical map
 - Restrain less affected upper limb for at least 6 hours per day, so training = 6 hours
 - Aims to reverse the “learned non-use”
 - Experiment (Nudo et al., 1996)

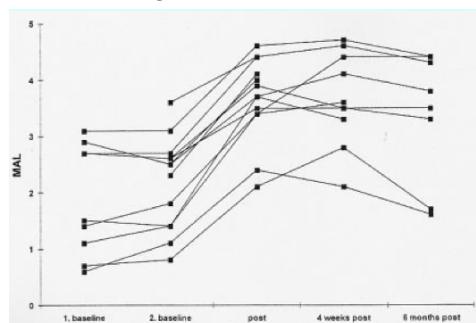


- M1 representing hand infarcted
 - Infarcted cortical area representing hand → decrease in ability to retrieve small food pellets, especially from small wells
- They were then put under intensive motor training

- Monkey who recovered spontaneously had a section of no response, larger infarction
 - Monkeys which recovered by rehabilitative training had a smaller areas of infarction
 - Cortical remapping
 - Training improved behavioral outcome
 - Training prevented further loss of adjacent areas around the infarct and can lead to the intact tissues to grow into the infarcted area
- Experiment (Liepert et al., 1998)

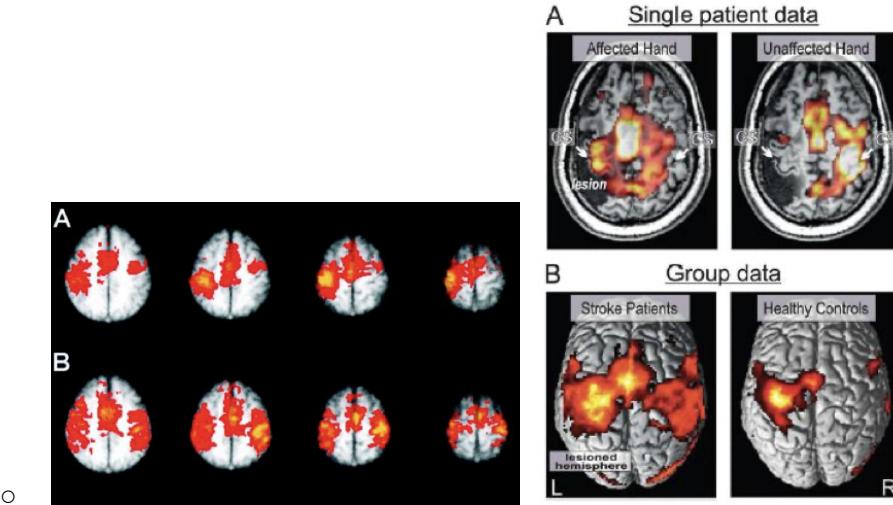


- Less used side (stroke affected side) had decreased cortical area, after training it improved



- Large improvement in cortical reorganisation after training
 - Behavioural gains maintained after training ceased
- Experiment (Qu et al., 2015)
- Tunnel cells present when there is apoptosis (indicator)
 - Tunnel cell number decreased after forced limb-use therapy while the number remains high for ischemia with no training
 - Forced-use therapy may decrease apoptosis
- Constraints in training
- **Timing of training important**
 - Training started very early can increase area of damage, reduce brain volume and result in poor motor outcomes

- However, there is no evidence for this in human adults
- Can't train early in development, damage intact corticospinal tract
 - Physiological stability required
- Movement of affected arm results in more bilateral pattern of activation in stroke patients
 - Bilateral activation

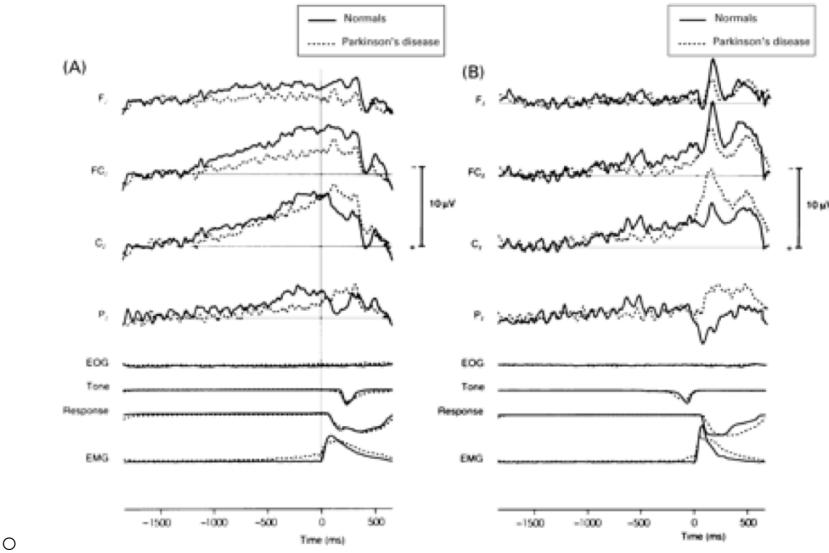


- Pharmacological
 - Fluoxetine → only one found to have effects on humans
 - D-amphetamine + therapy
 - (Ramic et al., 2006)
 - Mouse model
 - Performance on skilled forelimb reaching and ladder rung walking improved
 - Pellet retrieval improved
 - Improvement in task associated with axonal growth
 - D-amphetamine can induce increased expression of GAP-43 and synaptophysin which are associated with axonal growth and synapse formation
 - Significantly increased axonal growth in the deafferented basilar pontine nuclei
 - Goldstein et al., 2018
 - Humans, no effect
 - NogoA
 - NogoA is from a family of regeneration and growth inhibitory proteins
 - Present in myelin
 - Blocking of this lead to significant enhancement of regeneration, axonal sprouting and structural plasticity within CNS
 - Experiment (Papadopoulos et al., 2002)
 - Antibody against NogoA → IN-1
 - Ischemic lesion (permanent middle cerebral artery occlusion)
 - Control lesion groups ⇒ no difference between their rates of recovery Treated with the mAb IN-1 ⇒ rate of recovery was significantly different

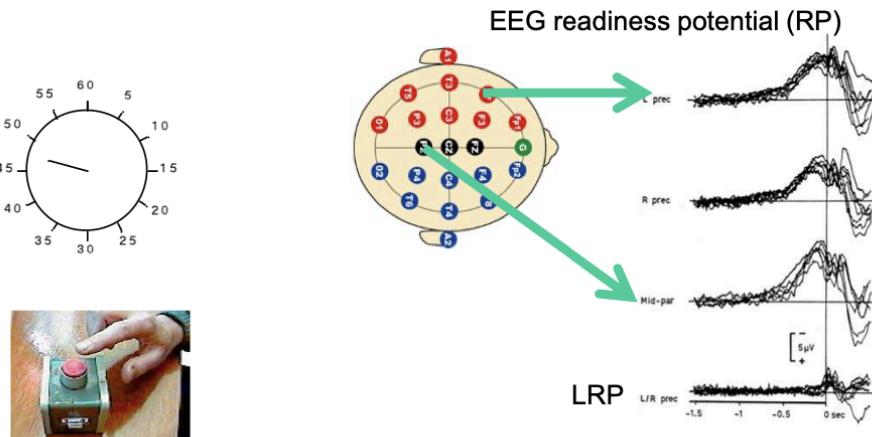
- 8 weeks following stroke, rats treated with the mAb IN-1 had fully recovered in terms of the time needed to obtain 20 pellets (99 seconds), and these results were not significantly different from baseline values
 - Rats treated with IN-1 also demonstrated more fibers crossing over from the contralateral primary motor cortex to the red nucleus to the ipsilateral side (the side with the infarcted cortex)
- BDNF
 - Brain derived neurotrophic factor → encourage growth of new neurons and support existing ones
 - (Nagahara and Tuszyński., 2011)
 - Mouse models shows promise
 - BDNF supports survival of existing neurons and encourages growth of new neurons
 - (Alcantara et al., 2017)
 - BDNF is reduced in humans following a stroke
 - Conversely aerobic exercise reduction of BDNF
- Induce neurogenesis
 - Implanting stem cells not doing too much

Volition

- Externally-triggered action
 - Movement in response to external stimulus
- Volition is internally generated actions
 - Aren't generated in response to an external trigger (e.g. sensory input)
 - Source of action comes from within
 - For example:
 - Actions with a random, unpredictable component
 - Acting out a complex sequence comprising several individual movements
 - Actions retrieved from long term memory
- Medial frontal cortex (medial wall) → almost no direct sensory inputs
 - Neurons in this area specifically activated not in response to external stimulus, but from individual wish to do an action
 - Not really responding to external stimuli
- Subcortical drive from basal ganglia to frontal motor areas
 - To SMA and pre-SMA
 - Major targets of basal ganglia loop
 - Driving medial frontal cortex to mediate voluntary action
- Experiment (Jahanshahi et al., 1995)
 - EEG electrodes placed externally on midline of head (roughly around the SMA, medial frontal region)
 - Epoch aligned to particular event
 - Recorded electrical activity throughout and averaged finding



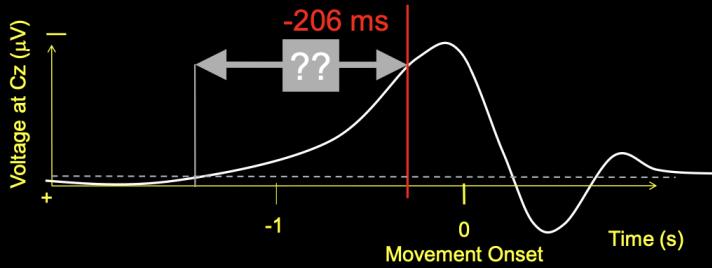
- Gradual build up of activity in frontal area of brain before actual movement
 - Symmetric activity over right and left hemisphere
- Experiment (Kornhuber and Deeke, 1966)
 - Discovered readiness potential
 - Asked healthy participants to make wrist flexion action whenever they wish to, just do it from time to time
 - Voluntary action disappear under experimental conditions (because experimenter tells participants what to do)
- Voluntary actions feel like they begin with conscious thought, but actually begin as deterministic brain processes
 - Experiment (Libet et al., 1983)
 - Invited to press button from time to time
 - Look at clock hand
 - Make a voluntary action from time to time and note position of clock hand when the participant first feels the urge to press the button
 - Can register movement of first conscious thought and movement time



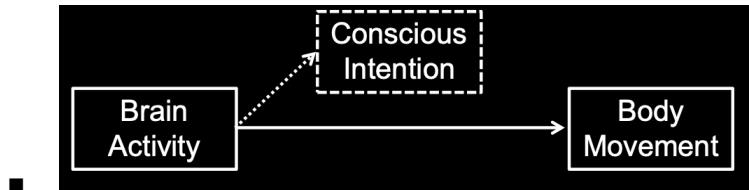
Advanced reading suggestion: RP-like properties of single neurons recorded in humans!
PMID: 21315264. 21315252

Conscious Intention and neural preparation for action

- Readiness potential preceding voluntary action
- W judgement : judgement of will/awareness of intention

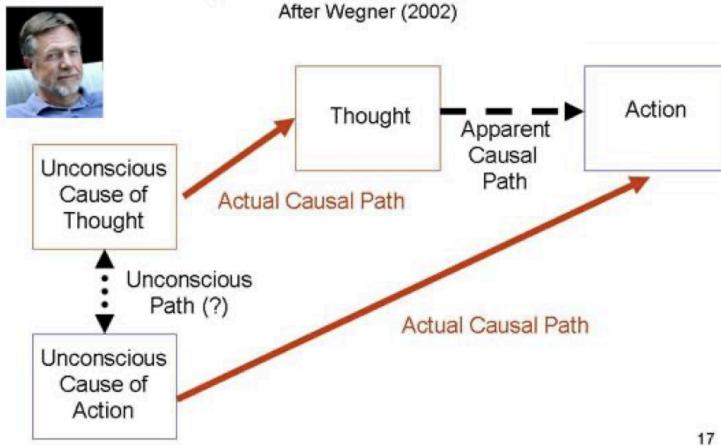


- - Graph: Negative up, positive down (voltage)
 - 0s is when movement begins
 - Actual time participants reported urge to move is ~206ms before actual movement
 - W judgement → judgement of will / awareness of intention
 - Libet thought that the gap (~206ms) allows time to stop action from happening
 - Gap between brain preparing for action and person becoming aware of the urge of move
 - Action generated by a neural circuit which is not yet conscious
 - Readiness potential occurs before conscious awareness of the thought
 - Brain begins to prepare for action before you are aware
- Neurosciences after Libet:
 - Brain activity leads to conscious intentions and body movement
 - Kind of like a CC on an email



Actual and Apparent Causation in the Experience of Conscious Will

After Wegner (2002)



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- - Unconscious brain activity causes action
 - We think thoughts causes actions, but it is an unconscious cause that leads to action
- Post-hoc retrospective confabulation
 - Brain activity causes body movements, you receive sensory feedback for body movement, then this sensory feedback makes you believe that you had a conscious intention to carry out the body movement
 - No real conscious experience before action
- Byproduct of brain activity
 - Conscious intention from direct brain stimulation
 - Traditional way of stimulation:
 - Electodes inserted into brain
 - Stimulate brain areas to map out cortex (stimulate specific regions causes specific responses in the patient e.g. laugh due to stimulation of limbic system)
 - Stimulating SMA (supplementary motor area) caused patient to feel urge to move (feeling that movement is about to occur)
 - Patient is experiencing something similar to a consciousness, but patient themselves has not moved
 - Opposes retrospective confabulation
 - Medial frontal cortex activity = feeling of impending action
- New research (Schugger)
 - Voluntary actions are the result of random neural noise, not result of any specific neural operation in the brain
 - Readiness potential is an artefact of averaging the random fluctuations that eventually is enough for action