

INTRODUCTION

- Many discoveries have been carried out since the second half of the *19th century* in the field of **neurology**
 - *Emil du Bois-Reymond* proved in 1848 the electrical basis of nerve impulse
 - *Korbinian Brodmann* identified a discrete brain region that still bears his name
 - some first serious attempts to **localize mental functions to specific locations in the brain** were made, mostly by studying the effects of injuries to different parts of the brain on psychological functions
 - in 1861, the French neurologist *Paul Broca* came across a man who was able to understand language but unable to speak, and later discovered that the man had damage to an area of his left frontal lobe now known as *Broca's area*
 - similarly, the German neurologist *Carl Wernicke* found a patient who, due to a stroke, could speak fluently but non-sensibly and was not able to understand spoken or written language, and later discovered that this patient had a lesion in the area where the left parietal and temporal lobes meet, now known as *Wernicke's area*
 - still, it was in 1890, when *Santiago Ramon y Cajal* introduced the idea of the **neuron**, namely a *discrete cell* which is the *primary computational unit of the nervous system*, that the field of **neuropsychology** emerged as an interdisciplinary field between *neurology* and *psychology*
- At the beginning of the *20th century*, the *American Pragmatism* led to *Behaviourism* to dominate until the '60s in the field of psychology
 - for *behaviourists* psychology is an objective and experimental branch of natural science which needs introspection as little as do the science of chemistry and physics, namely *psychology is the science that predicts and controls behaviour*
 - this trend became very successful thanks to its pragmatic and scientific approach and to the development of fundamental concepts as **classic and operant conditioning** based on original ideas of *Ivan Pavlov*
 - however, from the '60s on emphasis was put back on internal representations powered by the new concept of information processing, and this led to the birth of the trend of *Cognitive Psychology*
 - *Sperry* and *Gazzaniga*'s work on *split brain patients* in the '50s has been very instrumental in the progress of the field
 - the birth of *Cognitive Science* could be dated 1956, when a large number of cognitivists met at the MIT
 - *George A. Miller* presented its famous paper "*The Magical Number Seven, Plus or minus Two*"
 - *Chomsky* and *Simon* presented their findings on computer science
- Finally, the term **Cognitive Neuroscience** has been coined in 1976 by psychologists *Michael Gazzaniga* and *George Armitage Miller*
 - nowadays, *Cognitive Neuroscience* is an *interdisciplinary scientific discipline*, based on the fields of **neuroscience** and **cognitive sciences**, which studies the neural processes underlying cognition.

THE BRAIN ANATOMY

- The **Central Nervous System (CNS)** is divided into **four parts**: the *spinal cord*, the *brainstem*, the *cerebellum*, the *cerebrum*
 - with *PNS*, instead, we identify the **Peripheral Nervous System**, namely the set of sensory cells that are located over the body and are needed to send information to the *CNS*
- The **Cerebrum** is the most central part
 - it could be further divided into **four lobes**: the *frontal lobe*, in front of the head; the *parietal lobe*, on the upper part of the head; the *occipital lobe*, on the back of the head; the *temporal lobe*, on the side of the head
 - or it could be divided into **two hemispheres**, the *left* and the *right* one
 - they can communicate through the *corpus callosum*
 - this division is so that each hemisphere has to deal with specific functions and/or specific areas of the body

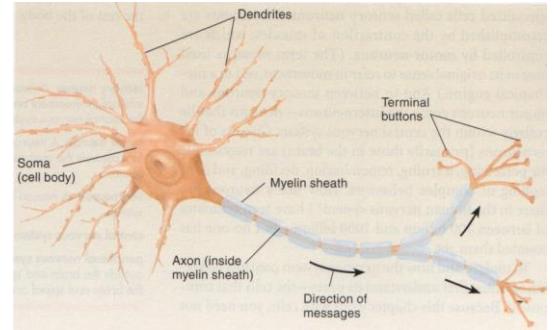
THE NEURON

- **Neurons** are special types of cells which are responsible for rapid communication between sensory cells, muscle cells and the brain
 - there are **three main processing types of neurons**
 - **Sensory**, which send information from the *PNS* to the *CNS*
 - **Motor**, which send information from the *CNS* to the *PNS*
 - **Interneurons**, which are located within the *CNS* and could be
 - *Local*, if they connect nearby neurons
 - *Relay*, if they connect circuits of local neurons to each other
 - also, there are **three main anatomical types of neurons**
 - a. **Bipolar**, having *one axon* and *one dendritic tree* (sensory neurons)
 - b. **Unipolar**, having *one stem* whose extremities fall both *outside the CNS*, with *dendrites* at the end, and *inside the CNS*, with *terminal buttons* at the end (sensory neurons)
 - c. **Multipolar**, having *one axon* and *many dendritic trees* (most common type in *CNS*)

→ e.g. *pyramidal cells*, or *pyramidal neurons*, are those that have been firstly studied by *Santiago Ramon y Cajal* and they are a type of multipolar neuron which can be found in areas of the brain including the cerebral cortex, the hippocampus, and the amygdala

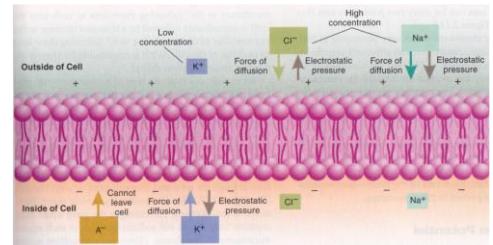
- The structure of a neuron is like the one following, where:

1. the **dendrites**, which are covered in *synapses*, receive the input information
 - most dendrites have **spines**, specialized structures that form one half of a synapse, and the formation and the removal of spines (known as *synaptic plasticity*) is a near continuous process that is hypothesised to be related to many behaviours such as motivation, learning and memory
 - the membrane under the synapse has many receptors that are able to detect neurotransmitters
2. the **soma**, namely the body of the neural cell, *integrates the information*
3. the **axon** carries the information very fast thorough the **myelin sheath**
4. the **axon terminals** pass the *information* to the adjacent neurons



THE ELECTROCHEMICAL BRAIN

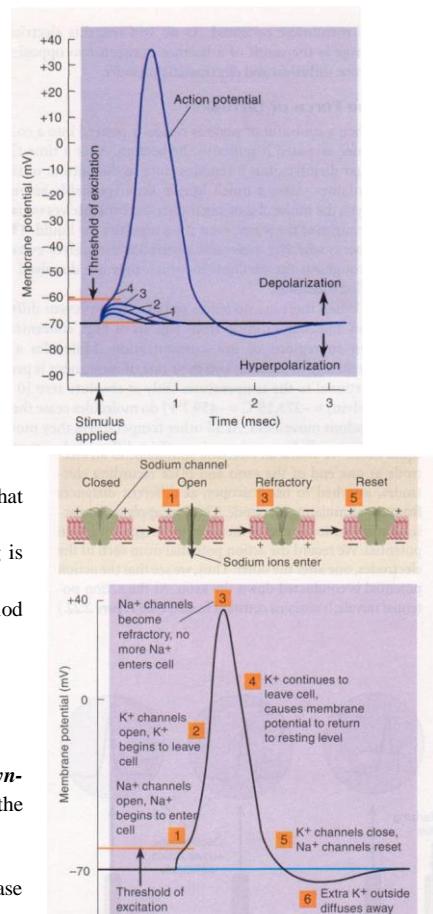
- The dynamic properties of neurons are derived from the fact that the brain is awash with electrically charged chemicals that exert pressures on each other and most notably on the cells' membranes
 - the *intracellular* and *extracellular fluid* contains **cations** (positively charged ions) and **anions** (negatively charged ions)
 - the cells' **membrane** is a *phospholipid bilayer*, which is relatively impermeable, and on its surface it has
 - **ion channels**, namely gated channels that can open or shut in order to allow some chemicals to pass through
 - **ion pumps**, namely active pumps that can exchange one chemical from the outside for another from the inside and vice versa
- The presence of *ions* and their movement from the outside of a cell to its inside and vice versa creates (and change) the so-called **membrane potential**
 - we indicate with *membrane potential* the difference of voltage between the two sides of the membrane of a cell, namely its outside and its inside
 - there are four ions which contribute to create this difference of potential, namely
 - *Sodium (Na^+)*, which is mainly outside the cell
 - *Chloride (Cl^-)*, which is mainly outside the cell
 - *Potassium (K^+)*, which is mainly inside the cell
 - *Organic Anions (A^-)*, mainly proteins and metabolic biproducts, which are only inside the cell
 - whenever a *channel* is opened, molecules will be subjected to **two forces** that tries to rebalance the *electrochemical* situation of the whole fluid are, namely
 - the **Diffusion**, a *chemical force* constraining to the uniform distribution of a certain kind of elements, which would push K^+ , Na^+ and Cl^- from their side to the other due to their difference of concentration
 - the **Electrostatic Pressure**, an *electric force* constraining to the uniform distribution of charges in a closed area. which would keep both K^+ and Cl^- to their sides due to the presence of the *membrane potential* while pushing Na^+ from the outside to the inside
 - in both cases, the organic anions are not subjected to the force of diffusion because their structure does not allow them to pass through the *ion channels*
 - as Na^+ would be pushed outside from both *diffusion* and *electrostatic pressure*, there is the need of another force represented by the **sodium-potassium pump**, which uses ATP to actively take *three Na^+ from the inside with two K^+ from the outside* and exchange their position
 - being this pump asymmetric from the point of view of electrical charge, it turns out that **the inside of the cell is negatively charged with respect to the outside** and this difference of potential, called **Membrane (Resting) Potential**, can be measured and it is almost *-70 millivolts*
- A message travelling along an *axon* takes the form of a *sudden change in the membrane potential*, best known as the **Action Potential (AP)**
 - if the stimulus is at or above a certain threshold, the *action potential is triggered*, and the **membrane potential is suddenly reversed**
 - what was once a negative difference, now becomes a positive one, leading to a new *difference of potential of +40 millivolts*



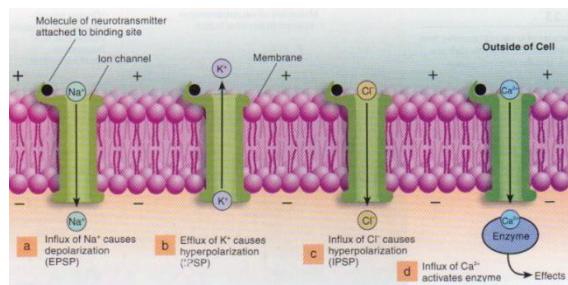
- In order to accelerate the propagation of the action potential, in vertebrates most axons are *myelinated*
 - the axon is surrounded by *myelinating glia* in order to form the ***Myelin Sheath*** through which the signal can propagate almost instantaneously (that is, without the need of a change in the action potential of the cells covered by the sheath)
 - when passing through the ***Myelin Sheath***, however, some of the potential gets scattered, with a resulting loss in magnitude
 - to avoid a complete loss of the action potential, some *gaps* known as the ***Nodes of Ranvier*** are put after regular intervals in which cells are not covered by *myelin*
 - in those gaps, cells are able to receive the action potential and *regenerate it* so that it could pass through another piece of *myelin* over the axon
 - this kind of propagation is called ***Saltatory Conduction***
 - the partial or total destruction of the *myelin sheath* can cause various problems such as the *multiple sclerosis*
- As a neuron can fire an *action potential* that has a definite value in magnitude, one can ask on what the threshold is based on, namely how the neuron can tell if a stimulus is weak or strong
 - the variable took into consideration is the ***rate of firing***, meaning that to a faster firing is related a more intense stimulus
 - anyway, the rate cannot exceed a thousand firing per second, being the refractory period of *1ms*
 - the summation across neurons allows for a great range of stimulus levels to be encoded

COMMUNICATION BETWEEN NEURONS

- A neuron can communicate to another one using its ***synapses***, which can be either ***electrical synapses*** or ***chemical synapses***, and are placed around the *dendrites* and receive information from the *terminal buttons* of the adjacent neuron
 - a *synapse* has *three main parts*
 - the ***pre-synaptic***, namely the *terminal buttons* of the previous neuron, which release vesicles containing ***neurotransmitters (NTs)***
 - the ***synaptic gap*** (or ***synaptic cleft***), namely a gap of 20nm full of extracellular fluid through which the *NTs* are diffused
 - the ***post-synaptic membrane***, which is a membrane with *ion channels* and *receptors for NTs*
 - the process of sending information from the end point of a neuron to the entry point of the successive one goes as follows
 1. the *AP* reaches a terminal button
 2. voltage-dependent ion channels open and let calcium ions (Ca^{2+}) enter from the cleft and bind with proteins, causing vesicles to attach to the membrane
 3. vesicles linked to the membrane push out the *NTs* contained in them
 4. *NTs* diffuse towards postsynaptic membrane and attach to binding sites of protein molecules, the *postsynaptic receptors*
 5. channels on the synapse open allowing ions to enter and leave the cell
- The ***post-synaptic*** plays the most important role into the collection of the information coming through a neuron, in particular
 - we can identify *two kinds of post-synaptic receptors*
 - the ***Ionotropic Receptors***, in which some *ion channels* get triggered from the binding of *NTs* that make them open and let ions to flow from the outside to the inside of the cell, changing the difference of potential
 - the ***Metabotropic Receptors***, which are more complicated and work through an indirect mechanism involving an enzyme placed on the membrane
 - *metabotropic receptors* allow a slower but more last-longing effect
 - furthermore, we can identify *two kinds of post-synaptic potentials*
 - the ***Excitatory Post-Synaptic Potential (EPSP)***, related both to *interneurons* and to *motor/sensory* ones, which ***depolarizes the membrane potential***, thus trying to create an inverse difference of potential
 - specific *NTs* used for *excitatory messaging*, generally ***Glutamate***, are released when impulses reach the *pre-synaptic*
 - eventually, they bind to the receptors of the *post-synaptic*, letting Na^+ ions to enter inside the neural cell and increase the potential
 - the ***Inhibitory Post-Synaptic Potential (IPSP)***, mostly related to *interneurons* only, which ***hyperpolarizes the membrane potential***, thus trying to restore the original difference of potential
 - specific *NTs* used for *inhibitory messaging*, generally ***GABA (Gamma-Aminobutyric Acid)***, are released when impulses reach the *pre-synaptic*
 - eventually, they bind to the receptors of the *post-synaptic*, letting Cl^- ions to enter inside the neural cell and reduce the potential



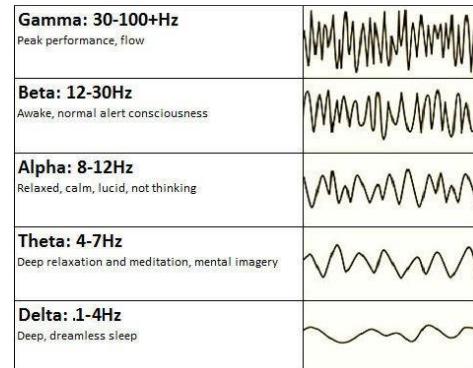
- which process occurs depends on which NT-gated ion channels are activated
- All incoming information is **integrated** by the neural cell (*soma*)
 - most *CNS* neurons receive thousands of synaptic inputs which activate different combinations of ionotropic and metabotropic receptors
 - the result of this neural integration is just one, whether the *Action Potential* is propagated or not
 - the **rate of firing** is determined by the relative *excitatory/inhibitory* activity at the synapses



OSCILLATORY FLUCTUATIONS IN THE MEMBRANE POTENTIAL

- Neurons are never truly “at rest”
 - individual depolarizing events happen at all times
 - their summation allows the signal to propagate synapse to synapse
 - many signals arriving at the same time would have a much larger effect with respect to the same number of signals arriving at different times
 - this is true both for *depolarization* as well as for *hyperpolarization*
 - the final result is an **ongoing fluctuation** in the dendritic membrane potential
 - this can be measured with an electrode in the extracellular space
- Rather than the activity of a single neuron, given their high density in electric properties in the extracellular space, what can be recorded is the so-called **Local Field Potential (LFP)**, i.e. the local region of cortex where these dendrites are located
 - even though the *LFP* is an aggregation of data from nearby neurons, it is often observed to fluctuate in an orderly oscillation
 - **oscillations** are so typical of the brain activity that they have been given names, and most scientists currently agree in associating them with specific functions:
- Neurons can manage to orchestrate individual single-channel events into a steady, predictable up and down rhythm thanks to multiple factors, mainly
 - each neuron is wired up with its neighbours in a certain way that facilitates the oscillatory behaviour of their ensemble
 - *inhibitory interneurons* tend to be connected one to each other in a way that allows the creation of synchronized loops via axonal connections in addition to sending signal to pyramid cells
 - as a consequence, pyramid cells tend to receive **synchronized hyperpolarized activity** facilitating rhythmic fluctuation on membrane potentials
 - e.g. a consequence of, say receiving a synchronized delivery of hyperpolarizing *GABA* 40 times per second, for example, is that the membrane potential of a pyramid cell will not actually remain at the steady -70mV but, more realistically, it will oscillate between -90mV and -50mV
 - given that neuron is much more likely to fire when the threshold is at around -50mV than -90mV, pyramid neurons have 40 windows per second in which they can fire
- Given the oscillatory nature of a neuron, we can conclude that there could be two ways for it to fire, namely
 1. time the delivery of its own action potential during a depolarizing phase of the membrane oscillation, say at -50mV
 2. receive many depolarizing inputs from its neighbours at the same time in order to maximize the chances to optimally depolarize and fire

→ it turns out quite evidently that a **synchronized activity of membrane oscillations** in different populations of neurons, referred to as **Phase Synchronization**, plays a crucial role in the smooth operations of the brain
- The **Electroencephalography (EEG)** is a non-invasive tool that measures the oscillatory and electrical activity in the human brain
 - differently from the **Electrocorticography (ECOG)**, which is an invasive tool as it must be placed under the skull, the *EEG* is made up of electrodes which are placed directly on the surface of the skull
 - the *EEG* does not measure neither the *AP* nor the *summation of APs*, indeed it measures the **Summation of Post-Synaptic Potentials (PSPs)**
 - it results from the *combined activity of a large number of similarly oriented pyramidal neurons* and requires *synchronous activity between those cells*
 - *EEG* is used to find an **Event Related Potential (ERP)**, namely a recorder signal which can be associated to a conscious event
 - being the brain never at rest, its activity always produces some kind of background noise which, however, almost annihilate itself, however, when a potential is synchronously fired between pyramid cells of the same area, the *EEG* can record a considerable anomaly in this background noise, resulting in a peak (and, eventually, in a subsequent bottom peak) in the *PSPs*

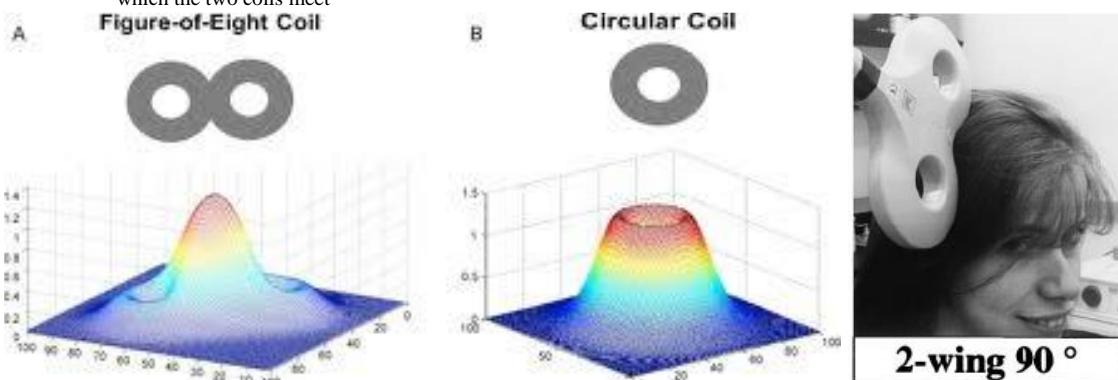


NEUROSTIMULATION

- **Neurostimulation** is the act of inducing certain kind of perceptions or movements into test subjects by the **magnetic or electric stimulation of the brain**
 - Jacques-Arsène d'Arsonval in 1896 and Silvanus Thompson in 1910 were the first two people to be able to *magnetically induce phosphenes* in human subjects by stimulation of the retina
 - a **phosphene** is the sensation of a ring or spot of light produced by pressure on the eyeball or direct stimulation of the visual system other than by light
 - In 1959, Alexander Kolin also succeeded in initiating muscle contractions in frog sciatic nerve, still this result was only peripheral and not in humans
 - so far, no motor response has been ever induced on humans
- In recent years, many tools for *neurostimulation* have been developed in order to be used both for therapy and for experiments
 - Those tools can be divided into
 - **invasive**, e.g. *Direct Cortical Stimulation*, *Deep Brain Stimulation* and *Electroconvulsive Therapy (ECT)*
 - **non-invasive**, e.g. *Transcranial Magnetic Stimulation (TMS)* and *Transcranial Electric Stimulation (tES)*

TMS vs TES

- The **TMS** is a non-invasive method of brain stimulation which has been developed from 1976 to 1985 at the *University of Sheffield* and uses short pulses of magnetic energy to induce a weak electrical current in underlying tissue
 - an electrical current passes through a coil and induces a magnetic field, which is perpendicular to the coil and, eventually, induces electrical current in the brain
 - a variant using two adjacent coils, the so-called *figure-of-eight coil*, is used to have a more precise stimulation in the area in which the two coils meet



- the *TMS* enables researchers to prove their theories about a correlation between brain activity and psychological evidences by designing experiments to produce a causal evidence linking the brain with specific behaviours
 - however, many safety issues must be checked before using the *TMS* over test subjects as this may lead to temporary discomforts and pains, such as headaches, seizures, and auditory problems
 - safety guidelines get published almost regularly
 - researches are also being carried out to determine whether the *TMS* could be safely and effectively used for clinical purposes as well
 - *rTMS (Repetitive TMS)* treatments are used to cure schizophrenia, tinnitus, seizure control and depression
- a **Sham TMS** has also been developed to produce the same acoustic and somatosensory sensations without effective concurrent magnetic field delivered
 - a **sham treatment** is the device equivalent of a placebo, indeed it is a fake stimulation used to test the benefits of the treatment by comparing the results between the actual group and the control group
- The **tES** is a more recent technique which involves the application of weak electrical currents (~1/2 mA) directly to the head for several minutes (*from 5 to 30*)
 - the stimulation is delivered by a battery driven current stimulator through a pair of electrodes, which generate an electrical field that modulates neuronal activity according to the modality of the application
 - *tES* induces a polarization that is too weak to elicit action potentials in cortical neurons, however, it presumably modifies the neuronal membrane potential, thus inducing a shift in the intrinsic level of neuronal excitability
- Preferring *TMS* or *tES* depends on many factors such as the reasons of their use, the cost and the issues of those devices, their effectiveness and so on, for example



- TMS has greater immediate risks like seizures and general kind of discomforts, while tES can cause, among the others, *headaches*, *skin irritation* and *nausea*
 - when using TMS, the prolonged exposure of the operator should be considered as well
- tES is cheaper, needs no external power supply and it because requires no trained operator to be applied, however its specifics have not been well studied yet
- their mechanisms are different, and they generate different reactions in the brain
 - **TMS** induces *action potentials*
 - **tES** causes *increased spontaneous cell firing*

NON-INVASIVE NEUROSTIMULATION METHODS

- **Single Pulse TMS** can be used to measure the excitability of the cortex or the corticospinal tract as well as producing “*virtual lesions*”
 - this has been used to create transient scotomas by stimulating the visual cortex
 - a *scotoma* is an area of partial degeneration in the field of vision, something similar to a blurry area in the field of vision
 - a similar effect can be achieved using TMS on blind people reading *Braille symbols*, indeed when the pulse was applied to the somatosensory cortex, people could easily read all the symbols, while when pulse was applied to the visual cortex they found more difficult to read symbols, meaning that their ability to read *Braille symbols* is encoded in the visual cortex and the TMS, virtually damaging that part of the brain, was obstructing their abilities
 - also, it can be used to generate *phosphenes*
 - *Resting Motor Threshold (RMT)* of the TMS causes *phosphenes* on subjects having closed eyes while *Active Motor Threshold (AMT)* of the TMS causes *scotomas* on subjects having opened eyes
- **Paired Pulse (PP) TMS** can be used to investigate inhibitory and excitatory circuits
 - depending on the *Interstimulus Interval (ISI)*, the second pulse can
 - *inhibit* the response, ISI of 1/6ms or 50/200ms
 - *facilitate* the response, ISI of 8/20ms
- **Repetitive TMS (rTMS)** performs a set of pulses repeatedly delivered at a certain frequency on a targeted brain area with effects on behaviour and brain physiology depending on the frequency of stimulation
- Some new paradigms are always being developed, for example
 - the **Patterned TMS**, used in *Theta Burst Stimulation (TBS)*
 - the **Rhythmic TMS**, used to study *oscillatory entrainment*
 - the **Cortico-Cortical Paired Associative Stimulation**, used for induction of network plasticity

	TMS	tES
<i>Spatial Specificity</i>	1 cm ³	Low (to be defined)
<i>Temporal Specificity</i>	Millisecond scale	Millisecond scale
<i>Safety</i>	Safe and non-invasive, with guidelines	Safe and non-invasive, no guidelines available
<i>Cost</i>	More expensive than tES	Affordable price
<i>Portability</i>	Heavy to handle, needs power supply	Handy and portable, battery operated
<i>Control</i>	Difficult to sham	Very easy to sham
<i>Application</i>	Research and Clinical settings	Research and Clinical settings
<i>Mechanism of Action</i>	Induces action potentials	Causes increased spontaneous cell firing
<i>Expertise</i>	Requires a trained operator	Easier to apply

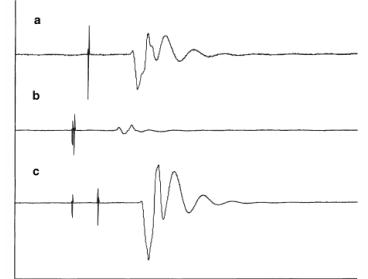


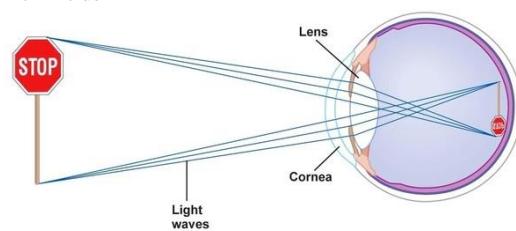
Fig. 2. Example traces demonstrating the response to paired pulse stimulation. Trace A is the response to a single control stimulus, Trace B shows the response to paired stimulation with a 1-ms interstimulus interval and Trace C shows the response to paired stimulus with a 15-ms interstimulus interval.

SENSATION AND PERCEPTION

- When identifying the *functions of the brain*, we should consider these main four
 - *Sensation*, which is the term given to the neural processes that correspond most closely to the concept of *detection*, indeed it occurs throughout the *translation of information* from the environment into a neural signal
 - *Perception*, which refers to the *identification* of features of what is being sensed and, generally, to its recognition
 - *Attention*, which can refer to many things but in *cognitive neuroscience* refers to how we mentally *prioritize* the perception of a certain stimulus among the others within our environment
 - *Action*, which can refer to isolated *acts* of motor control but also *goals* or *plans* that can be abstracted from isolated movements
 - it would be oversimplistic to consider these as *ordered steps*, as well as it would be oversimplistic to think of neural information as a strictly feedforward process, indeed the brain should not be considered as a passive receiver of information but an active system which is constantly representing the world
- When *sensing*, the brain translates the environmental information into signals, and this capability is achieved through the representation of that information into what it is known as the *Neural Code*
 - the *Neural Code* is a system for representing information in a format that is different from the physical properties of what is being represented
 - very little is yet known about this code, but it is evident that the brain uses action potentials and neurotransmitters to convey information
 - the act of encoding the information, i.e. to translate the *physical energy* into the *neural code*, is known as *Transduction*
- *Transduction* is carried out in different ways depending on the kind of stimulus
 - for *vision*, the *retina* transduces light of different wavelengths
 - for *audition*, the *cochlea* transduces mechanical fluctuations in air pressure
 - for *somatosensation*, receptors in the skin transduce different mechanical forces, chemical agents, and temperatures.

COGNITIVE NEUROSCIENCE OF VISION

- Vision is the most important sense for the perception of the world, and it is not by chance that it has been the most heavily studied in cognitive neuroscience
 - mechanically, our ability to see is guaranteed by the process of *Phototransduction*, in which some specialized cells called *photoreceptors* convert light into neural signals
 - in practice, *photoreceptors* convert electromagnetic radiation with wavelength between 400 and 700nm (i.e. the visible light) into an electric signal that causes a sudden change in the membrane potential of the cell itself
 - this change in the potential leads to a cascade of *Action Potentials* generated by the retinal ganglion cells, namely the output neurons of the retina which projects to the *Lateral Geniculate Nucleus (LGN)*, which is the relay centre in the thalamus for the visual pathway
 - the *thalamus* is the core part of the brain, which is placed in its centre
 - basically, the signal transduced by the retina is sent to the *LGN* which, eventually, sends the acquired information to the *visual cortex* and waits until the processed information will get back
 - when talking about vision, we mainly intend the concept of *Visual Field*, that is the spatial extent of everything that we can see in a certain moment
 - our *visual field* does not look all the same, indeed we have a sort of *centre of the gaze* in which we focus our attention and in which, consequently, our *acuity* (sharp vision) is maximized
 - this area is referred to as *foveal vision*, as it corresponds to the central part of the retina, which is in fact called *fovea*
 - our ability to give more emphasis to the objects in the *foveal vision* is due to the not uniform density of photoreceptors in the retina, where most of the receptors are grouped around the *fovea*
- The visual field can be divided either into *two halves*, the left and the right visual hemifields, or into *other two halves*, the upper and lower hemifields, or even into *four quadrants*, the left/right upper/lower hemifields
 - depending on how one or more quadrants are damaged, one can suffer from
 - *scotoma*, a smaller region within a single quadrant
 - *quadrantanopia*, the blindness of a whole quadrant
 - *hemianopia*, the blindness of a whole hemifield
 - also, due to the concave shape of the retina, the light reflecting objects below the point of fixation will be projected into the upper retina and vice versa, whose consequence is that in *VI* (the *primary visual cortex*) everything is flipped with respect to the visual field, indeed
 - the left hemifield is related to the right hemisphere (and vice versa)
 - the upper visual field is related to the lower visual cortex (and vice versa)



- practically, the spatial organization of *V1* reflects the spatial organization of the retina as well as its functional topography mirrors the functional topography of the retina, we refer to this as the *Retinotopic Organization of V1* or ***Retinotopy***
 - another important characteristic of *retinotopy* is that it will be sensitive to stimulation within a larger or smaller portion of the visual field, namely it will have a larger or smaller ***receptive field***, depending on what portion of the retina a neuron represents
 - neurons placed in a region which receives input from the fovea will have larger receptive fields with respect to neurons placed in a region which receives input from peripheric areas
 - this property leads to the so-called ***Cortical Magnification***, namely the fact that the representation in the fovea is higher than in the rest of the visual field
- The visual cortex is able to recognize objects and shapes by *constructing a description which is based on more elemental information*
 - there are at least six ***transforms of elemental information*** into visual features: orientation selectivity, direction selectivity, higher acuity, binocular disparity, convergence, construction of colour from three cone types
 - basically, information processing in *V1* is carried out by these neurons which behaves as ***feature detectors***
 - for example, *direction selectivity* is achieved by considering the lag between the firing of two adjacent neurons responding to the same visual stimulation, thus the information built that the object seen in that part of the visual field is moving in a particular direction
 - the primary visual cortex is organized in ***hypercolumns***, i.e. a grid of orientation columns that together represent every orientation (and other features as well) that could fall within a receptive field
 - ***hypercolumns*** are organized in pinwheels, so that the centre is not sensitive to orientation.
 - also, for each ***feedforward axon***, going from the *LGN* to *V1*, we have from 3 to 9 ***feedback axons***, going from *V1* to *LGN*
 - such a disproportionate balance between feedforward and feedback projections is due to the fact that anticipatory wave activity back to *LGN* requires a lot of circuitry, indeed organisms use their sensory input to formulate new hypotheses in higher brain centres which must be brought back to the core

Retinal image



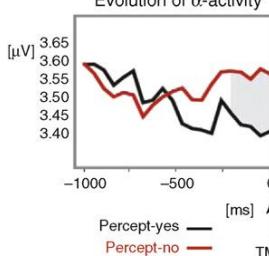
Cortical map



ALPHA RHYTHMS AND VISUAL PERCEPTION

- The ***Alpha Rhythm***, i.e. the oscillation of *potential* related to brain waves between 8 and 12 Hz (the *alpha waves*), was traditionally assumed to be associated with areas of the cortex that are not processing information
 - indeed, the belief was that a high presence of those waves implied either a resting or an idling/lazy state of the given area, e.g. the visual cortex when eyes are closed, while with eyes opened the visual system would get the message "something to do" and get out of the idling mode, producing higher-frequency waves
 - an alternative account is that ***the brain may configure itself in different states*** to optimize performances on the currently prioritized task by selectively inhibiting irrelevant items
 - e.g. visual perception is usually (not always) prioritized when eyes are open, thus signals coming from other senses are bypassed by the brain
 - therefore, instead of indicating an idling state, *alpha waves* could represent a ***threshold*** under which signal arriving to that specific area is ignored
- ***Spontaneous Fluctuations in Posterior α-Band EEG Activity Reflect Variability in Excitability of Human Visual Areas, Romei et al., 2008***
 - the experiment was tested over fifteen subjects that were blind-folded and subjected to many *TMS impulses on the lower-left area of the visual cortex* while their cerebral activity was recorded through an *EEG*
 - of all the subjects, just nine were able to perceive phosphenes (obviously around the upper-right corner of their visual field) from the *TMS impulse* at least once and, for each of them, the machine intensity was calibrated so that they could perceive the phosphene with *50% of probability*
 - though it is known that to an increase in the *TMS intensity* corresponds a higher chance of perceiving the phosphene, each person has their own sensitivity and their respective thresholds
 - those nine subjects were then subjected to a new round of *TMS impulses* and their cerebral activity recorder through an *EEG*, eventually the data related to the ***alpha band potential in the second before the application of the TMS stimulus*** was extracted via *FFT (Fast Fourier Transform)* and grouped depending whether the phosphene had been seen (***P-yes***) or not (***P-no***)
 - the results exhibited no interesting differences between the *P-yes* and *P-no* case except for those related to the ***three electrodes placed in the lower-left area of the head***
 - indeed, in these cases, as we can see in the plot, ***a lower intensity in the alpha-band led to the perception of the phosphene while a higher intensity led to no perception***
 - many other tests involving various aspects were made to prove the causal relationship between the fluctuation in the *alpha band* and the perception of the phosphene, for example
 - the same test with *TMS impulse* applied in different areas or with different orientation of the magnetic field shown no significant difference

Evolution of α -activity

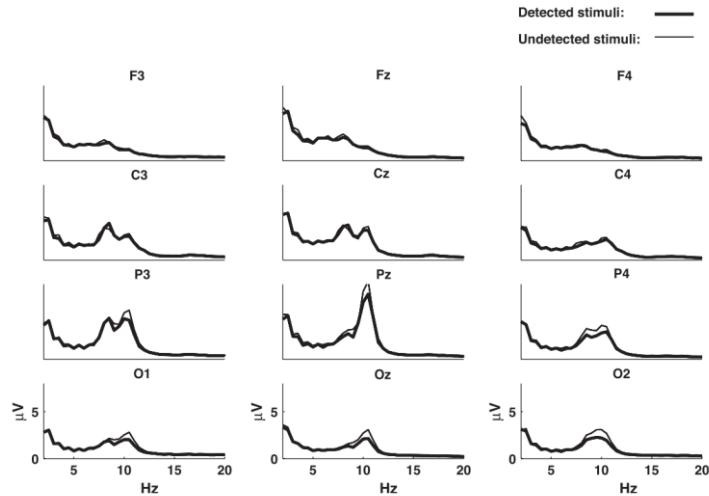


- a test using multiple *TMS impulses* at constant *ISI* shown that the perception of the phosphene was related neither to the ability of predicting the impulse nor to a higher attention of the subject, indeed the probability of getting a *P-yes* remained steady on 50% over subsequent impulses
- a test on eye movement shown that there was no direct relationship between voluntary or involuntary modulation of the eyes and both the perception of the phosphene and the fluctuations in the alpha band
- a test on the sequences of *P-yes* and *P-no* by subjects shown that the results were not influenced by any voluntary action, indeed those sequences were consistent with the outcomes of Bernoulli process as they were following a binomial distribution
- results of this experiment provided further support to the alpha/excitability hypothesis and for an *inverse relationship between oscillatory alpha band activity and cortical excitability*, proving that alpha activity is not a passive idling state but instead reflects the momentary state of cortical excitability
 - practically, the *potential* of alpha waves sets a *threshold of perception*, indeed whenever the fluctuation reaches a low point (around $3.45\mu V$) neurons fire even when receiving a sufficiently powerless stimulus that, in case of high potential (around $3.60\mu V$), is not powerful enough to activate the action potential of the neurons in the area and, therefore, the stimulus gets bypassed

CONSCIOUS PERCEPTION AND BRAIN OSCILLATION

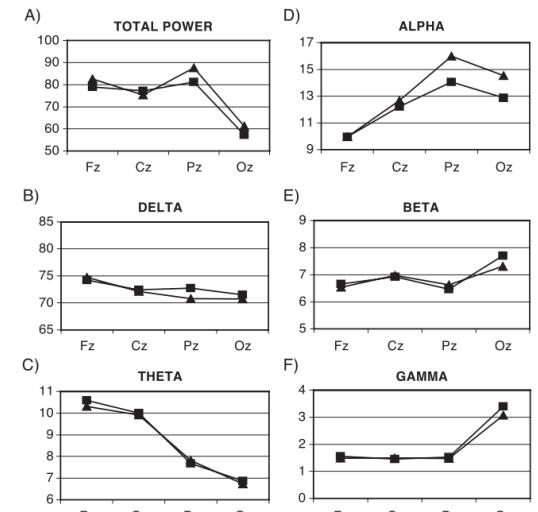
- ***Alpha Rhythm of the EEG Modulates Visual Detection Performance in Humans, Ergenoglu et al., 2004***

- the experiment was tested over *twelve subjects* that, during *EEG* recording, were undergone a *peri-threshold visual stimulus*, namely a laser beam which was flashed always in the same location and calibrated for each subject in order to be perceived 50% of the times
 - *peri-threshold* means that the stimulus is around the threshold, indeed in this case it is calibrated to be perceived half of the times
- oscillatory activity in theta, alpha, beta and gamma frequency bands was recorded by the *EEG* before the flash of the laser and the resulting power of these bands was calculated by means of *FFT* relatively to the electrodes placed in the *Frontal (F)*, *Parietal (P)*, *Central (C)* or *Occipital (O)* area
 - prestimulus *FFT* shown significant differences between detected (*P-yes*, indicated by the *square* in the plot) and undetected (*P-no*, indicated by the *triangle* in the plot) trials, particularly when considering *alpha band* oscillations in the *parietal* and *occipital* area
- again, this study proves that spontaneous fluctuations in prestimulus oscillatory alpha power determine whether we will consciously perceive or not visual stimuli on a trial by trial basis, in other words alpha power sets the detection threshold of a sensory system at any given point in time
 - lower alpha power prior to stimulus onset is associated with higher chance of visual detection (*low threshold*) while higher alpha power prior to stimulus onset is associated with lower chance of visual detection (*high threshold*)

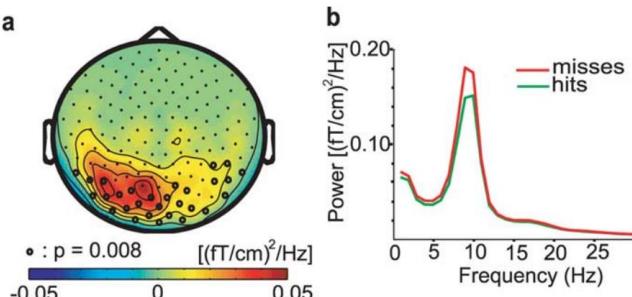
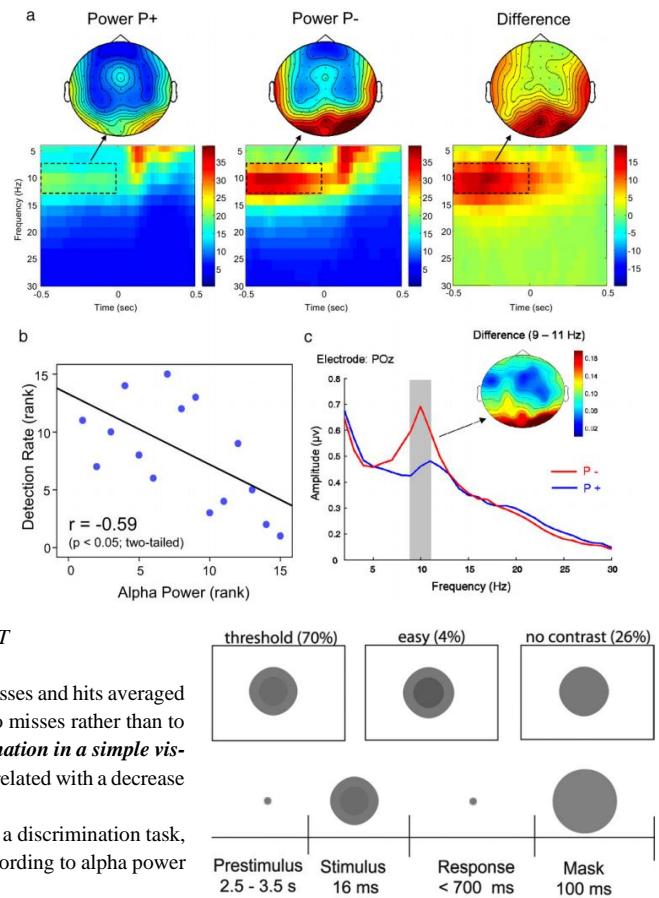


- ***Prestimulus Alpha Oscillations Predict Between Subjects Visual Perception Performance, Hanslmayr et al., 2007***

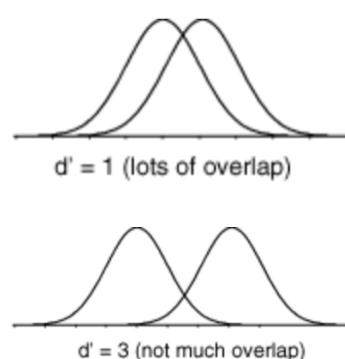
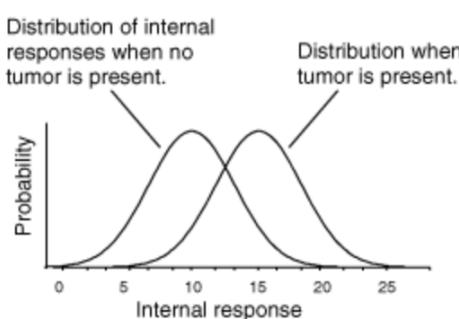
- the experiment was tested over *thirty subjects*, fifteen *perceivers (P+)* and fifteen *non-perceivers (P-)*, that were undergone a *peri-threshold visual stimulus* during *EEG* recording
 - the visual stimulus was presented very shortly (*some milliseconds*) after the appearance of a fixation cross in the led screen and, eventually, masked with other similar stimuli for some more time
 - in particular, the stimulus was a randomly chosen letter in { p, q, b, d }, namely the same symbol subjected to a reflection over the axis, and the mask was made up of the superimposition of all the four letters
 - *perceivers* were those subjects able to recognize the input stimulus in 50% of the cases, while *non-perceivers* never managed to guess it



- oscillatory activity in theta, alpha, beta, and gamma frequency bands was recorded and calculated by means of *Time-Frequency Analysis*
 - the plot shown that the only noticeable difference between **P+** and **P-** can be found in the power of *alpha bands* in a time window of 500ms prior to the presentation of the stimulus and also, from the scalp maps, that **alpha power was strongest at parieto-occipital electrodes**
- the results of this study show that prestimulus oscillations can be used to predict perception performance between subjects and *synchrony in the alpha frequency band, as measured by power, inhibited visual perception*
- **Prestimulus Oscillatory Activity in the Alpha Band Predicts Visual Discrimination Ability, Van Dijk et al., 2008**
 - the experiment was tested over *eight subjects* that, during *MEG recordings*, were undergone a *peri-threshold small disc superimposed to bigger discs of different contrast* flashed always in the same location to be perceived 50% of the times
 - the *threshold stimulus* was presented 70% of the times, while an *easy stimulus* 4% of the times and a *no-contrast stimulus* the remaining 26%
 - oscillatory activity was recorded and calculated by means of *FFT*
 - this study shows that
 - from a topography of the difference in the alpha band between misses and hits averaged over subjects, *stronger alpha power* is significantly correlated to misses rather than to hits, namely that **alpha power correlates with contrast-discrimination in a simple visual task** in the sense that an increase in posterior alpha power correlated with a decrease in discrimination ability
 - there is no correlation between alpha power and *reaction time* in a discrimination task, indeed no significant difference emerged for *RT* when sorted according to alpha power quartiles



- anyway, something known so far is that **the probability of detecting a visual stimulus increases when prestimulus alpha power is low**, but the reason for this increment could be explained by two different mechanisms, either an *effective change in perceptual sensitivity* or rather a *change in the response criterion*
 - in other words, it might still be that this increment in the probability of detection when alpha power is low could be due to the fact that people will tend to more likely report a percept, independently of whether the stimulus was effectively there
- The best way to explain this last issue is to refer to what has been known since 1954 as the **Signal Detection Theory (SDT)**, namely the means to measure the ability to differentiate between information-bearing patterns (*stimuli/signals*) and random patterns that distract from the information

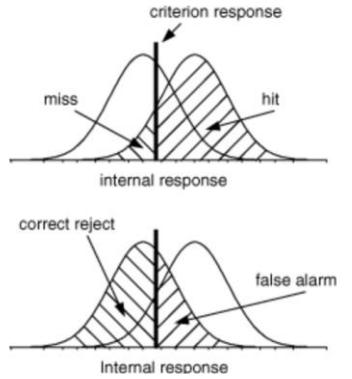


FUNCTIONAL BENEFITS OF INHIBITION

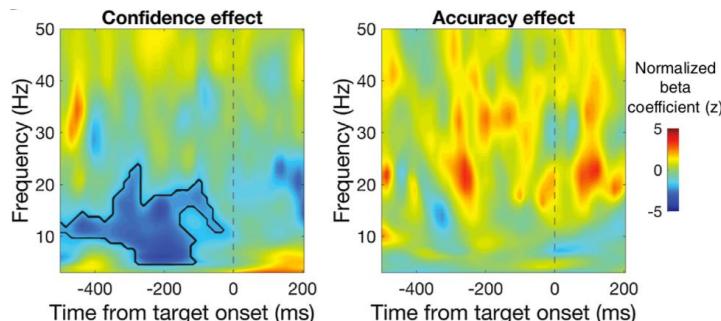
- Little is yet known about the **functional benefits of the inhibition of stimuli** from the visual cortex due to the high power in the alpha band, however some theories have been proposed and experimented in recent years
 - one advantage might be the **possibility to reduce the flow of information which could interfere with processing in higher order areas**
 - e.g. if we are directing our attention to something that is at our left, we perceive it more with our left side, that is with our right hemisphere, therefore the alpha power will decrease on that hemisphere while increasing in the other one in order to bypass most of the information coming from the right direction, being that the one we are not interested in

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- the **discriminability index**, namely $d' = \frac{\text{separation}}{\text{spread}}$, is a value depending both on the *separation* and the *spread* between the noise-alone and the signal-plus-noise curves of a certain signal
 - discriminability is made easier either by increasing the separation, i.e. strengthening the signal, or by decreasing the spread, i.e. reducing the noise, and in either case the result is a **less overlap between the probability of occurrence curves**
- as a result of *SDT*, we know that placing a vertical line (*response criterion*) we represent a threshold between the distributions of the two signals, we would have **no responses before this line**, leading to a correct non-activation of the neurons in case of no stimulus (*correct reject*) but a wrong non-activation in case of low enough stimuli (*miss*), and **responses after this line**, leading to a correct activation in case of a stimulus (*hit*) but a wrong activation in case of a powerful enough noise (*false alarm*)
 - in 2016, Limbach and Corballis observed that subjects of their experiment were adopting a **more conservative criterion when alpha power was high**, and this is a proof that **prestimulus alpha power is not related to d'** but to the *response criterion*



- **Prestimulus Alpha-Band Power Biases Visual Discrimination Confidence but Not Accuracy, Samaha et al., 2017**
 - the experiment was developed taking in mind the idea that changes in criterion had been linked to changes in subjective awareness reports, therefore **prestimulus alpha may impact confidence ratings** in a discrimination task, but **should not affect discrimination accuracy**
 - indeed, when cortical excitability is non-specifically increased, namely when there is a *low power in alpha bands*, neurons representing the presented stimulus as well as those representing the non-presented alternative should *both increase their firing rates by the same amount*, leaving discriminability between the two unaffected, but if **confidence is driven primarily by evidence in favour of the decision rather than the balance of evidence for both possible choices**, then confidence will be systematically higher when cortical excitability is higher despite no change in accuracy
 - this practically means that our accuracy in the perception of a stimulus is not influenced by the prestimulus alpha band, indeed the *ratio between yes/no responses from our neurons remain unchanged*, what changes instead is the *absolute value of yes/no responses*, which gives us a **greater confidence whenever there is a low power in the alpha band prior to the stimulus**
 - in order to prove this theory, *ten participants* were subjected to a *two-choice orientation-discrimination task*, namely they were asked to say whether the stimulus they had been undergone was rotated left or right
 - the *peri-threshold stimulus* was so that participants could guess the right orientation in almost 80% of the cases
 - then, after their prestimulus activity was recorded through *EEG*, they were asked to say how much they were feeling confident about their answer on a scale from 1 to 4
 - scales having an even number of possible answers are used to detect even small changes in perception, indeed, here subjects are forced to express an opinion which, otherwise, would likely fall in the neutral answer
 - results of a single trial regression of confidence and accuracy on power revealed that **prestimulus low-frequency power prior to target onset was negatively correlated with confidence ratings, but not discrimination accuracy**

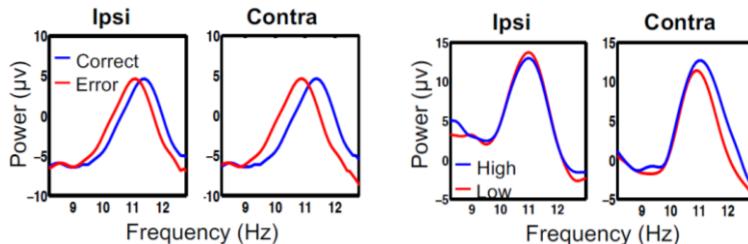
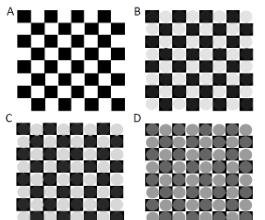


- these findings show that **oscillatory alpha power is responsible for subjective rather than objective measure of perception**, and also that it is possible to *dissociate confidence from accuracy solely on the basis of prestimulus brain states measurable with EEG*
- Proven that *alpha power* codes solely for the subjective experience of confidence during a perception discrimination task, one could ask what is the neurophysiological correlate which accounts for perceptual accuracy, that is **which factor is related to a higher or lower probability of a correct detection**
 - what has been proven by *Samaha's experiment* is that a *high alpha power* is related to a low cortical excitability (*active inhibitory state*) and a subsequent low confidence (*conservative response*) in discrimination tasks, while a *low alpha power* is related to a high cortical excitability and a subsequent high confidence (*liberal response*)
 - however, sinusoidal waves are defined not only by their *power*, namely its *amplitude peak to peak*, but also by their *frequency*, namely the duration of one oscillatory cycle
 - in general, we know that high-frequency waves, i.e. *beta* and *gamma*, are linked to higher performing states of the brain, while low-frequency ones, i.e. *theta* and *delta*, are linked to lower performing state of the brain such as idling/relaxation states or even deep dream states
 - this is enough to let us think that low-frequency waves are *slower* than high-frequency ones, and that they can carry less information

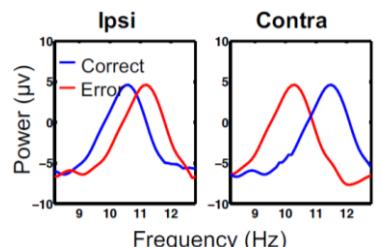
- coming back to the *alpha band*, one could think that *slower alpha rhythms* ($\sim 8\text{Hz}$) are related to slower real-time info updates and lower temporal resolutions, which result in a smaller amount of information, while *faster alpha rhythms* ($\sim 12\text{Hz}$) are related to faster real-time info updates and higher temporal resolutions, which result in a greater amount of information
 - thus, *slower prestimulus alpha rhythms indicate a lower accuracy while higher prestimulus alpha rhythms indicate a higher accuracy*
 - proving this relationship has been the aim of *Di Gregorio's experiment*

- ***Neural Correlates of Subjective vs. Objective Measures of Perception, Di Gregorio et al., submitted***

- the experiment was tested over *twenty-four participants* that were subjected to a visual stimulus, presented either in the left or right part of a screen, consisting in a chessboard with possibly superimposed grey circles calibrated in order to be perceived *50%* of the times
 - these are some examples of the stimulus presented to each subject depending on their sensitivity, from the *catch stimulus (a)* to the *maximum contrast stimulus (d)*
 - after the presentation of a stimulus, participants were asked to say if they had seen the grey circles and how much they were confident about their answer on a scale from *1* to *4*
 - when extracting data from the *EEG*, a distinction was made between *contralateral* (i.e. on the opposite side of the brain) and *ipsilateral* (i.e. on the same side of the brain) alpha power in order to show the differences between hemispheres when presenting the stimulus at the left or right side of the screen
- in the first step of the experiment, the stimulus was presented with *no previous cue* for the participant about which side it would appear
 - first of all, prestimulus alpha power was analysed, from which it turned out that *lower alpha power in the contralateral area were related to a higher confidence*, while no correlation was found between confidence and alpha power in the *ipsilateral area*
 - this is, again, a proof of the ability of prestimulus alpha power of a certain area to predict level of subjective confidence independently of the accuracy obtained in the discrimination task
 - then, *prestimulus alpha frequency* was analysed as well, from which it came out not only that *faster alpha frequency were related to correct responses* but also that *frequency did not correlate to subjective confidence*



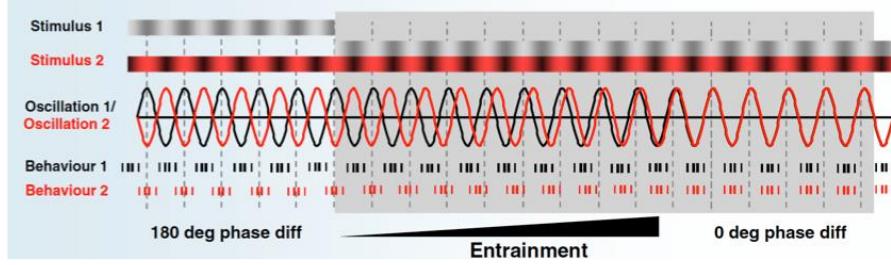
- this proves the ability of *prestimulus alpha frequency* to predict the level of objective accuracy (and not the confidence) in discrimination tasks
- so far, the experiment provided data in which subjects have limited predictive capacity of what will be happening next, therefore the next step of the experiment tries to answer whether there is an interplay between confidence and accuracy when the location of the stimulus presentation can be anticipated, namely when a *predictive cue* is presented to the subjects before the stimulus
 - the cue is shown on the screen before the stimulus in form of an arrow pointing either to the left or to the right depending on the side of the screen in which the chessboard, which is the stimulus, will appear
 - in this case, an analysis of the prestimulus alpha power proved not only a *negative correlation between power and confidence in the contralateral area* (the same as before), but also a *positive correlation between power and confidence in the ipsilateral field* rather than no correlation at all
 - this result shows that, when a valid cue is proposed to the subjects, the alpha power of one hemisphere is actively lowered while the alpha power of the other one is actively enhanced by the brain as a response to the focus of attention on the related hemifield and the subsequent "voluntary" inhibition of the other one
 - as well, an analysis of the prestimulus alpha frequency proved that the difference of frequencies between *correct* and *wrong responses* was still present in the ipsilateral area and *even more enhanced in the contralateral one*
 - this shown when a valid cue is proposed to the subjects, their brain actively enhances the frequency of alpha waves, particularly in the area in which the stimulus is expected to appear (but also, slightly, in the other one) as a response to this acquired knowledge
 - in conclusion, these findings show that
 - when spatial occurrence cannot be predicted (*neutral cue*), spontaneous fluctuations of alpha power in space may serve as generative perceptual processes by which we guess where the next stimulus will be presented (the so-called *perceptual hypothesis*), in particular
 - low cortical excitability (*highly synchronized alpha power*) represents the null hypothesis that no stimulus is going to appear at that location, known as the *conservative criterion*



- high cortical excitability (*desynchronized alpha power*) favour the alternative hypothesis that the stimulus will appear at that location, known as the *liberal criterion*
- on the other hand, ***alpha speed accounts for the spatiotemporal resolution of the visual system and predicts its accuracy*** by setting the pace of visual temporal units refresh rate and the updating of sensory input information
 - *faster alpha oscillations* will lead to *higher sampling resolution per time unit* allowing *more accurate spatiotemporal information decoding* due to a very efficient neural coding
 - *slower alpha oscillations* will lead to *lower sampling resolution per time unit* allowing *less accurate spatiotemporal information decoding* due to a less efficient neural coding
- instead, when contextual information is provided allowing for ***top-down prediction of the to be attended location***, the visual system ***optimizes the top-down control of alpha power*** to allocate faster sampling rate (*faster alpha frequency*) exclusively at the attended location in order to match what we think we see with what is effectively out there

FROM CORRELATION TO CAUSATION

- TMS has always been widely used to carry out experiments about perception and neuroscience in general, in particular thanks to its ability to generate stimuli that can be controlled and calibrated, and its effectiveness is also due to the fact that the evoked potentials generated by TMS could be measured at the cortical level by an online EEG/MEG recording
 - this interactive approach of ***combining transcranial stimulation with an encephalography*** turns out to be very useful as it allows to explore where, when, and how TMS affects a functional network during a cognitive task, for example interacting with ongoing oscillations and test their functions
 - however, some precautions should be taken in order not to let the two devices interfere and, eventually, return corrupted data
 - the same kind of issues come up as well with other devices for transcranial stimulation have been used, such as tACS namely *Transcranial Alternate Current Stimulation*, which is similar to the TMS but, instead of affording the stimulation via a magnetic field, it uses electric current to accomplish the stimulation (in fact, it is a kind of tES)
- Exploiting the combination of these two devices, the studies presented so far (e.g. *Romei's experiment of phosphene induction using TMS bursts*) were able to evoke a correlative evidence associating a certain brain frequency to a given behaviour
 - showing a *correlation*, however, does not imply a *causation*, indeed those studies ***did not provide any information about a causal relationship between alpha bands and functional activities of the brain*** because they could not explain if this represents a mere epiphenomenon or a causal role in brain processes
 - nonetheless, this step from a *correlational approach* to a *causal approach* can be done by shifting from a mere observation of the phenomena to an ***active manipulation of brain oscillations aimed at their entrainment*** (synchronization), something that can be achieved with the help of ***rTMS (rhythmic TMS)***

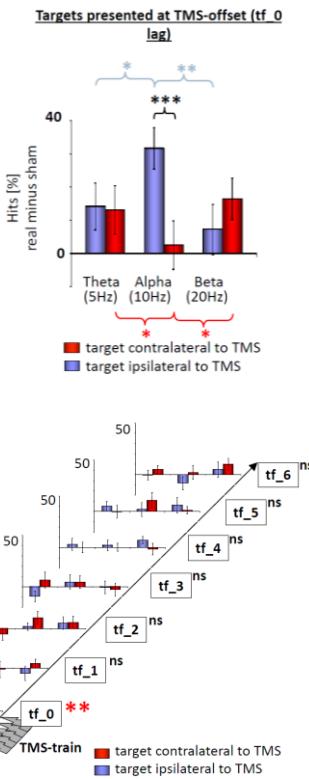


- while a *correlative mapping* asks whether certain oscillations reflect mental (receptive) states and if they can be used to predict future perception, a *causal mapping* asks whether it is possible to actively induce oscillatory brain activity patterns to generate mental states and modulate functions
- Finally, an important point has to be made clear about the meaning of perception, how it is correlated to alpha bands, and how this correlation can lead to two different situations depending on the experiment
 - so far, we said that *prestimulus alpha power* is linked to subjective confidence while *prestimulus alpha frequency* is linked to objective accuracy, and as perception is something completely related to an individual, it should be evident that ***perception can be measured in function of subjective confidence***, while accuracy has nothing to do with it as it is not related to an individual's awareness
 - anyway, depending on the kind of experiment, perception can be measured in two different ways, in particular
 - for experiments involving a ***perception task***, those in which there are stimuli involving ***a single option*** and subjects are asked to say ***whether they perceived it or not*** (e.g. they have seen the phosphene or they have seen the laser on the screen), it is the act itself of perceiving that measures the confidence, indeed objective accuracy and subjective confidence are merged together and it is not possible to evaluate them separately, being the response completely biased by the perception of the subject (that is, there is no way to know if the subject has unconsciously seen the stimulus but not strongly enough to be consciously perceived)
 - for experiments involving a ***discrimination task***, those in which there are stimuli involving ***multiple options*** and subjects are not asked to say if they perceived it but ***which option did they see*** (e.g. they have seen a chessboard with grey disks or without them), we are able to distinguish between accuracy and confidence as subjects are forced both to give a positive answer on the task and to rate their confidence

ENTRAINING BRAIN OSCILLATIONS TO PROVE CAUSALITY

- **Biasing Perception via Pre-Stimulus Short-Train TMS, Romei et al., 2010**

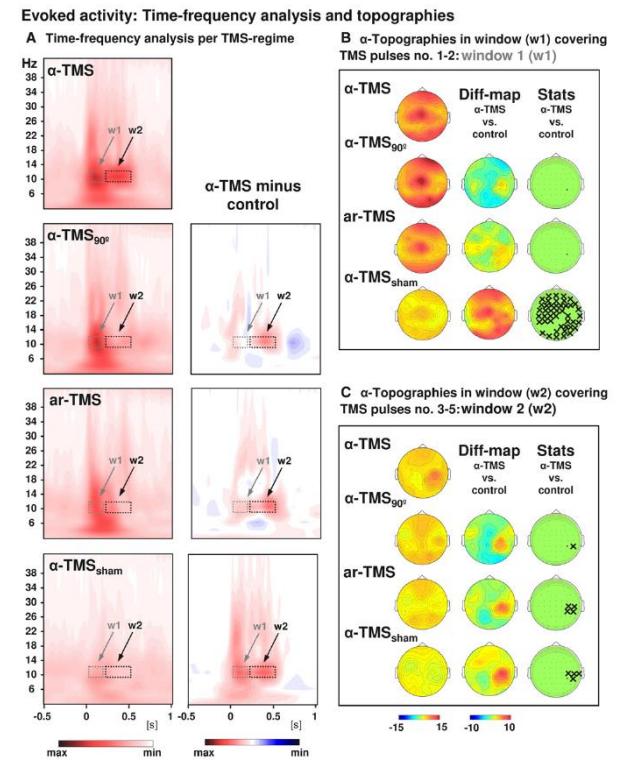
- once proven the correlation between prestimulus alpha band and certain mental states, the aim of this new experiment was to **prove causality** by the exploitation of *rTMS bursts*, calibrated to that the frequency of the stimulation would coincide with the natural frequency of alpha bands in the targeted brain area, to **entrain oscillations at the frequency of stimulation** and eventually show that **subjects perception could be biased in desired directions** thanks to this train
 - indeed, provided that the entrainment can be achieved, this synchronization in the alpha bands should enhance their power, eventually leading to a drop in the subject's perception
- the experiment was tested by undergoing participants **five subsequent, rhythmic TMS burst** and asking them whether they perceived a phosphene or not
 - *rTMS* exposition was done for several minutes in order to cover different tests involving different parameters, such as
 - *two stimulation sites* (parietal vs occipital)
 - *two stimulation sides* (left vs right hemisphere)
 - *three stimulation frequencies* (5Hz, 10Hz, 20Hz)
 - *two target locations* (ipsilateral vs contralateral)
 - the total number of runs was, then $2 \times 2 \times 3 \times 2 = 24$, each one involving 7 time frames for *EEG recording*, then the experiment was repeated with a sham *TMS* in order to get data normalized over the control condition
 - results shown that, independently from site and side, the stimulation led to frequency and spatially specific perceptual consequences, showing that the entrainment had been successfully achieved and that its consequences were particularly noticeable for frequencies around 10Hz respectively to those around 5 or 20Hz, also
 - as one would expect, with targets located in the contralateral area subject's detection was reduced, while with targets located in the ipsilateral area subject's detection was enhanced, meaning that entrainment of waves in one hemisphere entailed a desynchronization in the other one
 - the effect lasted no more than 3.5 seconds, indeed no evident change can be seen in the last time frames



- this study proved that ***alpha-activity is not merely an epiphenomenon as it can shape perception***, indeed posterior alpha-oscillations have an active role in perceptually relevant tuning of visual areas for sensory selection, and also that it is possible to bias (both to inhibit and enhance, depending on the hemisphere) an individual's visual perception by means of rhythmic transcranial stimulation

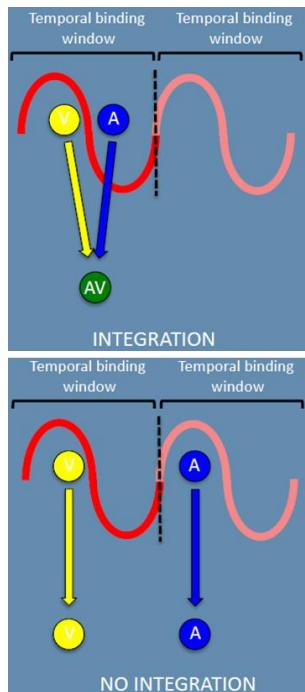
- **Rhythmic TMS Causes Local Entrainment of Natural Oscillatory Signatures, Thut et al., 2011**

- while the previous experiment found an (indirect) correlation between *rTMS bursts* and **brain oscillation entrainment** by means of subject's perception measured as the accuracy of their responses to the presentation of a peri-threshold visual stimulus (a phosphene, in that case), this one aimed at proving a **direct correlation between rTMS bursts and brain oscillation entrainment** by showing how this transcranial stimulation is able to change the synchronization measuring the potential generated by the brain through an *EEG recording*
 - indeed, as well as the previous one the experiment was tested by undergoing participants many **subsequent, rhythmic TMS burst**, but in this case subjects were not asked to perceive anything (instead, the *TMS* was specifically calibrated and placed in certain areas not to generate phosphenes on subjects)
 - in order to prove the effectiveness of the study, many different sessions were done, each one changing one parameter so to have meaningful control data
 - in the *real session*, named *α-TMS*, pulses were given at a fixed rate α (calibrated with the subject's individual alpha frequency, *IAF*) in order to prove the entrainment of this α -rhythm
 - in the *control session* named *ar-TMS*, the same number of pulses were given arrhythmically in order to prove that no entrainment could be achieved in this way
 - in the *control session* named *α-TMS_{90°}*, pulses were given with the coil perpendicular to the stimulated area in order to prove that less entrainment (or no entrainment at all) could be achieved

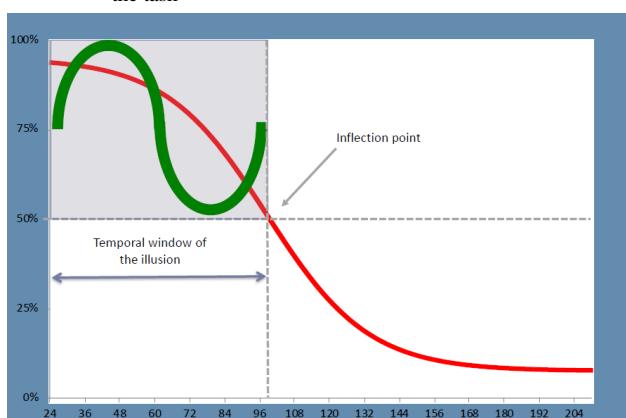


- in the *control session* named α -TMS_{sham} pulses were given with a *sham TMS* in order to prove that entrainment was not achieved because of external factors independent from the *TMS* stimulation itself
- a final *control session* used a *fake head with no brain activity* on which α -TMS pulses were applied in order to show that the presence of synchronized alpha waves was not a mere consequence of the rhythmicity of the pulses themselves but, instead, a consequence of the ability of pre-existent waves (those from the brain) to entrain with the incoming ones (those generated by the *TMS*)
- results shown that, after the first two bursts that equally entrained each band from the brain in the real session as well as in the control sessions excluding that one using a *sham TMS*, meaning that the first *TMS* bursts have an impact on brain activity independently from its rhythmicity, from the *third burst on* the entrainment focused on **alpha bands only** and, in particular, just **around the stimulation area**
 - also, the entrainment effect started to vanish after less than one second
- this study represented the *first, direct proof of frequency entrainment*

BRAIN OSCILLATIONS AND MULTISENSORY PERCEPTION

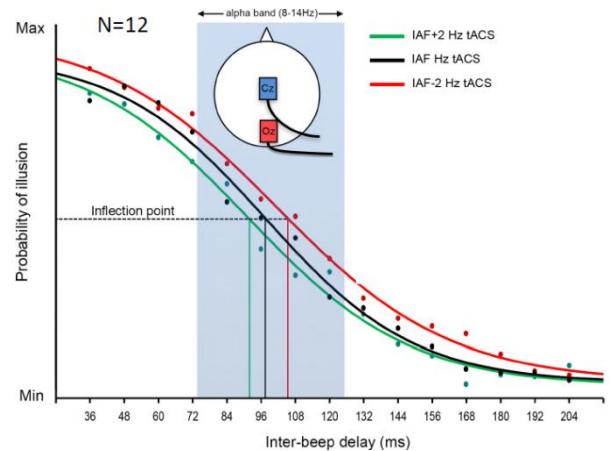


- Whenever multisensory stimuli are presented in a small enough time-window, they get **integrated**, i.e. processed during the same “time step” by the brain
 - it has been shown that the time-window of integration related to visual stimuli largely varies across individuals, in fact this time window is strictly related to the frequency of the brain oscillations, and in particular to alpha waves
 - on average, alpha waves are around 10Hz, thus the time-window is as large as an alpha cycle, which would be of 100ms
 - however, this frequency varies from 8 to 14Hz across individuals, leading to time-windows of 125 to 70ms
 - anyway, within an alpha cycle, stimuli are **perceived as simultaneous**, meaning that the brain is kind of sampling information coming from different senses at the rate of alpha frequencies
 - this is what happens in the so-called **double flash illusion**, where a single flash on the screen comes with two subsequent auditory stimuli (*beeps*)
 - in case the two auditory stimuli are presented within an alpha cycle, the brain will get fooled and subject will report to have seen *two flashes on the screen* as well as two beeps, while if the two stimuli are separated enough in time, then subjects will report to have seen a *single flash* and two beeps
 - also, it has been shown that auditory stimuli have the ability to **phase reset the alpha cycle**, namely when the brain receives an auditory stimulus, it prepares to receive a visual stimulus as well by resetting the phase of alpha waves
 - as a result, because each alpha wave restarts its phase, they get synchronized in order to respond quickly to the incoming visual stimulus
- **Individual Differences in Alpha Frequency Drive Crossmodal Illusory Perception, Cerere et al., 2015**
 - the experiment achieved two distinct results with two distinct procedures, respectively showing the *correlation* between alpha frequencies and the integration time-window and the *causal relationship* between the two
 - *correlational approach* → manipulation of behavioural variable and observation of covariation of the studied physiological variable
 - *causal approach* → manipulation of physiological variable and observation of its impact on behaviour – in this case, manipulation of brain oscillations
 - at first, participants were subjected to a behavioural task, namely the *double-beep illusion*, while recording their alpha frequencies by *EEG* in order to find the *peri-threshold inter-beep delay* related to each participant so that they got fooled half of the times
 - results shown that the peri-threshold delay was exactly as long as the average alpha cycle for each participant, indeed it has sense to assume that the length alpha cycle can vary a little bit according to a normal distribution, thus sometimes the brain will integrate the information and some other times not with the same probability
 - once measured their duration of the alpha cycle and, as well, their **Individual Alpha Frequency (IAF)**, each participant was subjected to three sessions of *tACS* (*transcranial alternating current stimulation*), respectively at frequency *IAF - 2Hz*, *IAF* and *IAF + 2Hz*, in order to entrain their brain oscillations and see how this entrainment would reflect on their ability to respond to the task



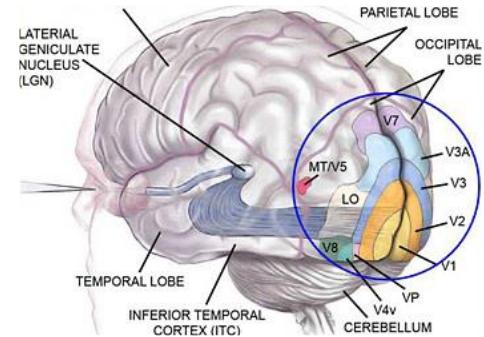
- results shown that when entraining to a frequency higher than the *Individual Alpha Frequency*, namely when increasing the frequency of the alpha waves, participants were less prone to get fooled by the illusion as result of the reduction of the length of the integration time-window, on the other hand, an entrainment to a lower frequency with respect to the *IAF* enlarged the temporal window of the illusion, resulting in a lower accuracy
- in conclusion, we can say that the brain builds up the **best sensory representation within its physiological constraints**, and these constraints can be measured in the form of alpha oscillations, which represent the temporal unit of sensory processing within the visual system and could serve as a cortical scanning mechanism that cyclically gates perception

- Another, final proof of causal link between alpha activity and perception, can be found in an experiment by Trajkovic in which 51 participants, subdivided in three groups of 17 people, were asked to respond to a discrimination task consisting in the detection of a peri-threshold visual stimulus and subsequent confidence rating
 - participants of the three groups were subjected to *rhythmic TMS* stimulation, respectively at *IAF – 1Hz* (slower frequency), *IAF* (same frequency, resulting in higher power) and *IAF + 1Hz* (higher frequency)
 - also, a sham control was made for each subject
 - results shown that, those subjected to a higher frequency stimulation reported higher scores in the objective accuracy while those subjected to a lower frequency stimulation reported lower scores, instead, as regards subjective confidence, a difference with respect to control condition was noticeable only in the group stimulated with the same frequency
 - again, this can be seen as a proof that ***alpha power accounts for subjective confidence*** while ***alpha frequency accounts for objective accuracy***

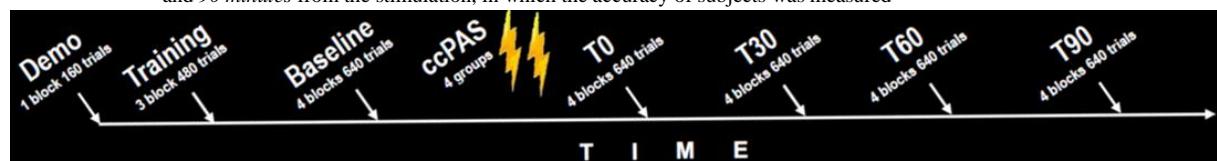
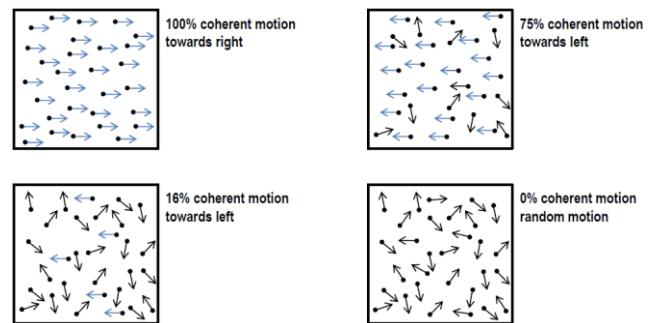


THE PLASTIC HUMAN BRAIN

- With **Hebbian Plasticity** we refer to the theory by *Donald Hebb* according to which repetitive activation of neuronal circuits can induce long-term changes in subsequent responses generated by synapses in many regions of the brain
 - such plasticity of synaptic connections is regarded as a cellular basis for developmental and learning-related changes in the central nervous system, namely persistent activities tend to induce lasting cellular changes in order to increase its stability whenever the activity is repeated again
 - e.g. when an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased
 - namely, every time A successfully excites B, it is like their connection gets strengthened so that, the next time, there response will be faster
 - evidences of this theory have been found in macaques and humans, in particular with respect to the role of *feedback projections* from secondary to primary visual areas in visual awareness as well as the state of the primary visual cortex itself
 - e.g. visual motion perception tasks, namely tasks in which subjects have to detect the direction of the motion of certain objects or group of objects, are particularly related to the state of V1 and to the feedback projections coming from V5 (motion visual area) to V1
 - indeed, the brain processes motion by comparing the state of a group of neurons with the state of the same group of neurons in the previous "time unit" and, thus, checking if and how this state has changed

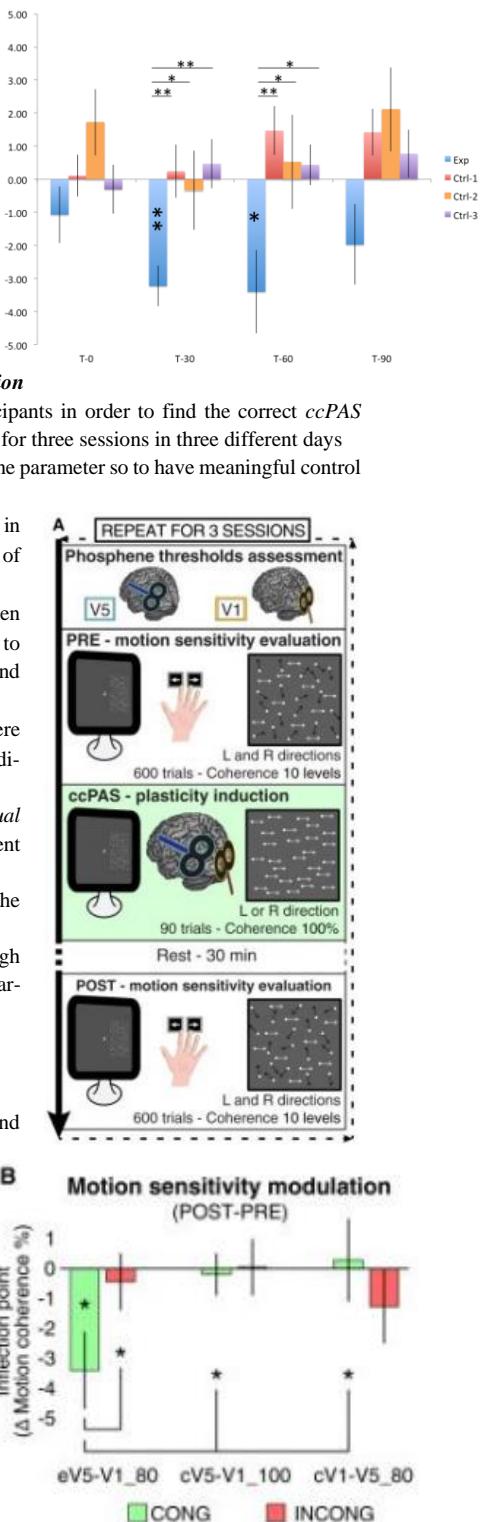


- Empowering Re-entrant Projections from V5 to V1 Boosts Sensitivity to Motion, Romei, Chiappini, Hibbard, Avenanti, 2016**
 - The aim of this experiment was to causally test *how the feedback connectivity from motion visual area (V5) to V1 affects sensitivity to motion by directly modulating this connectivity* using a novel ccPAS paradigm
 - ccPAS, namely *cortico-cortical paired associative stimulation*, is a paradigm in which two TMS pulses are fired in two different areas of the brain, possibly with a delay with the two pulses
 - The 32 participants of the experiment were split in *four groups* and, while recording their brain activity through EEG, they were undergone a *visual motion perception stimulus* (both in the right hemifield and in the left one with the same probability) in which particles were moving either left or right
 - at first, the motion coherence of the particles was specifically calibrated so that each participant would guess the right answer about 75% of the times
 - then, each group was subjected to a different kind of stimulations, each one changing one parameter so to have meaningful control data
 - in the *experimental group*, named *Exp_{V5-V1}*, 90 paired pulses were given in V5 at first and in V1 later with a delay of 20ms, where 20ms is on average the time that it takes a stimulus in V5 to reach V1
 - in the *direction control group*, named *Ctrl_{V1-V5}*, the same pulses were given in V1 at first and then in V5 in order to show a correlation with the direction of propagation of the stimulus in the brain
 - in the *timing control group*, named *Ctrl_{0ms}*, the same pulses were given in V1 and V5 at the same time in order to show a correlation with the duration of propagation of the stimulus in the brain
 - in the *placebo control group*, named *Ctrl_{sham}*, the same pulses were given from V5 to V1 with 20ms delay but using a *sham TMS*
 - after a demo session in which subjects were trained to respond to the task and a *baseline session* to measure the accuracy prior to the stimulation, it followed the ccPAS stimulation and, eventually, other *four sessions*, respectively after 0, 30, 60 and 90 minutes from the stimulation, in which the accuracy of subjects was measured



- in practice, the aim of the ccPAS session is to increase the connectivity between neurons in V5 and neurons in V1 by simulating a fake propagation of the potential from V5 to V1, namely to simulate the training of neurons in V5 to have a higher sensitivity with respect to motion perception tasks in order to increase the performance of members of the experimental group
- results shown that *only members of the experimental group* exhibited an improvement in the motion perception task (expressed in terms of Δ percentage of coherent motion correctly guessed 75% of the times) particularly 30 and 60 minutes after ccPAS, while the effect was started reducing after 90 minutes

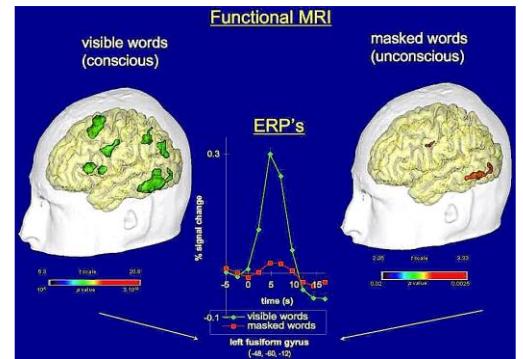
- this can be seen as the proof that applying *ccPAS* over two functionally connected visual regions improves visual processing depending on the parameters of stimulation (e.g. directionality, timing, ...), and that empowering reentrant connections from V5 to V1 implicated in the conscious perception of visual motion boosts visual motion sensitivity
- ***Strengthening functionally specific neural pathways with transcranial brain stimulation, Chiappini, Silvanto, Hibbard, Avenanti, Romei, 2018***
 - Similarly to the previous experiment, this one aimed at directly modulating this connectivity using the *ccPAS* paradigm, still, in this case, the *ccPAS* stimulation was performed at a peri-threshold intensity while participants were made to see the stimulus itself with particles going 100% either towards the left or towards the right in order to ***strengthen just the specific neural pathway coding for that specific direction***
 - At first, a *phosphene threshold assessment* was carried out on each of the 16 participants in order to find the correct *ccPAS* intensity, then these participants were split in *three groups* and the procedure repeated for three sessions in three different days
 - each group was subjected to a different kind of stimulations, each one changing one parameter so to have meaningful control data
 - in the *experimental group*, named *e_{V5-V1_80}*, 90 paired pulses were given in V5 and then in V1 with 20ms of delay at an intensity in the amount of 80% of the previously measured phosphene threshold
 - in the *intensity control group*, named *c_{V5-V1_100}*, the same pulses were given at an intensity in the amount of 100% of the phosphene threshold in order to show that the effectiveness of the stimulation is correlated with a precise and localized activation of certain neurons
 - in the *direction control group*, named *Ctrl_{V1-V5_80}*, the same pulses were given at first in V1 and then in V5 in order to show a correlation with the direction of propagation of the stimulus in the brain
 - eventually, 30 minutes after the stimulation, participants were subjected to the *visual motion perception task* and their accuracies both in case the direction was congruent to the one presented during the stimulation or incongruent to that
 - results shown an increment in the accuracy only in the experimental group and only in the tasks congruent with the stimulation
 - again, this can be seen as a proof that it is possible to induce neural plasticity through the *ccPAS* protocol and, in particular, that this induced neural plasticity can be targeted on specific neural pathways
- From these (and other studies), we could conclude that
 - Functional connections are highly plastic in the brain and follow Hebbian rules, and ***ccPAS can temporarily induce this Hebbian-like plasticity in the visual system*** as well as targeting and enhancing the efficiency of specific pathways which can be functionally selected
 - Feedback connectivity allows for efficient processing of information, in particular re-entrant connectivity from higher order to early visual areas is functionally relevant to motion perception
 - e.g. ***re-entrant V5-V1 pathways carry function-specific information for the processing of motion direction***
 - Cognitive Neuroscience developments have allowed for causal testing of such principles in the human brain



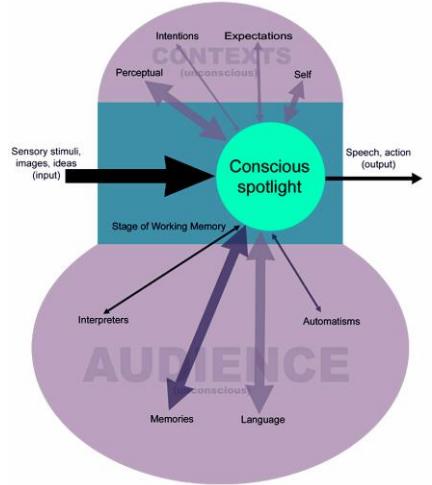
CONSCIOUSNESS & AI

- As **consciousness** is regarded as a subjective personal experience, it seems that it could hardly fit in the scientific view of the world
 - However, many theories are now considering **consciousness** as a biological evolutionary function promoting complex flexible and adaptive behaviours
 - indeed, it has the precise functional role to allow a more flexible response when automatic actions are unsuitable
 - Still, one big open question is related to the way consciousness arises
- The **Global Workspace Theory (GWT)**, proposed by *Bernard Baars* in 1988, tries to pinpoint the causes of the appearance of consciousness
 - Consciousness is seen as a supremely functional biological adaptation used for exercising *global coordination and control*
 - it is essential in integrating perception, thought and action, in adapting to novel circumstances, and in providing information to a self-system
 - e.g. if you unconsciously make a speech error, you will not be able to act upon to correct, but as soon as you become aware of it you can fix it because consciousness creates global access to further unconscious resources
 - According to *GWT*, a piece of information is conscious if it is *broadcast widely to many areas of the unconscious brain*
 - in fact, our consciousness can access just a small amount of processes in our brain, while there are many other unconscious neural processes going on with us having no control on them
 - *Baars* refers to this as the "**Theatre Hypothesis**"
 - consciousness act as a "bright spot" on the stage
 - it is surrounded by a fringe of events that are only *vaguely conscious*
 - the unconscious audience, sitting in the dark, receives information broadcast from the bright spot
 - behind the scenes there are numerous unconscious contextual systems that shape the events happening in the bright spot
 - Far from being just a metaphor, the theatre hypothesis is heavily grounded in psychology and neuroscience knowledge
 - the metaphorical elements can be easily linked to cognitive concepts and the interactions between themselves are based on the *GWT* architecture
 - the *bright spot* is the *attention*, namely that mechanism that allow us to focus on a small amount of things that we find more interesting
 - the *backstage* is the set of *neural processes* actively going on during all day and even in the night
 - the rest of the stage is the so-called *working memory*, namely the global workspace through which conscious and unconscious processes can communicate by sharing information
 - also, the working memory capacity, namely the number of items at a time that are dealt within that global workspace, seems to be strictly related to the famous 7 ± 2 number from George Armitage Miller's 1956 paper
 - basically, consciousness acts as a gateway, providing global access to any part of the nervous system
 - From the *GWT* we can conclude that **consciousness is not an epiphenomenon, nor it is mysterious, but is instead a working part of the cognitive system** which has very definite effects and functions, such as
 - providing access to mental lexicon, memories, and the "self" system
 - recruiting processors for ongoing tasks, facilitating executive decisions, and enabling voluntary control over automatic actions routine
- Since 2006, *Stanislas Dehaene* extended the *GWT* to the **Neuronal Global Workspace Theory** by showing how sensory information gets selected to be broadcast throughout the cortex
 - The idea is that, inside the brain, a collection of specialized unconscious processors compete for access to the limited capacity *Global Workspace*
 - information can be widely broadcast to other brain areas and this brain-scale broadcasting creates a global availability that results in the possibility of verbal or non-verbal reports and is experienced as a conscious state
 - in practice, many different brain regions both send and receive numerous projections to and from a broad variety of other, distant brain regions, and this allowing the neurons there to integrate information over space and time so that it could converge onto a single coherent interpretation
 - In *Dehaene's 2001 paper Cerebral Mechanisms of Word Masking and Unconscious Repetition Priming*, a number of subjects were undergone a series words on a screen while recording their brain activity through *functional magnetic resonance imaging (fMRI)*
 - some of the words were clear (*unmasked*) while some other were covered (*masked*) by other visual stimuli around them
 - it turned out that the two different groups of words activated completely different neural pathways, proving that masked words can unconsciously activate part of the cerebral networks for word processing and, as a consequence, there must be two different ways in which the brain process input information, depending on the fact that the input is clearly understandable or should be undergone a sort of pre-processing
 - Also, through *Neuronal GWT*, the *theatre metaphor* could be turned into several testable models, and with respect to it, it can be said that

- only the bright spot on stage is the consciousness, which is related to *selective attention*
 - in particular, consciousness is very limited in capacity
- sensory inputs, coming from outside the theatre, compete for access to the conscious bright spot
- the stage corresponds to the working memory, which is shared by processes
- all other features like long-term memory or the automatic processes of language are in the audience, while perceptions and intentions are events going on in the backstage
- still, both of these are unconscious, and sometimes they get access to the working memory and, as result, have effects on the bright spot

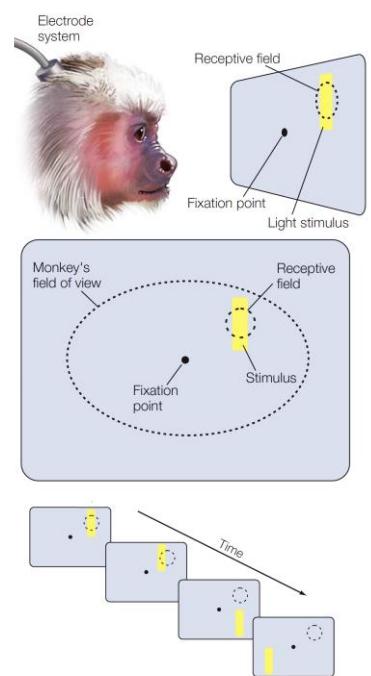


- Future perspectives regarding *cognition* and *neuroscience* are believed by many researchers to be strictly related to the development of new technologies and, in particular, those concerning *artificial intelligence*
 - Almost every aspect of consciousness is still unknown, but thanks to new tools to study cerebral activities with a high resolution and new technologies able to simulate the inner functionalities of the brain, we will probably be able to make new discoveries in the next years
 - Still, two main fundamental questions are open bring to many discussions
 1. if you could look right inside the brain and see everything that was happening there, would you then understand consciousness?
 2. if you could exactly and precisely replicate connections as you find them right inside the brain into an artificial modelling network, would you then have reproduced a conscious network?



SELECTIVE VISUAL ATTENTION

- **Selective Visual Attention** is one of the most fundamental cognitive functions
 - (*Selective*) Attention is a mechanism used by the brain to *reduce the cost of processing information*, indeed, due to the high energy cost of neuronal activity, the brain has not enough capacity to process each object in a scene, thus uses this adaptive behaviour to focus on a smaller amount of information which is most relevant to the animal's goals
 - e.g. this is the cause of the so-called *change blindness*, whereby it is difficult to spot small changes in two similar images, because our attention is focused on just a subset of objects which are more important from a behavioural point of view
 - In particular, we are interested in its *visual* part as *vision is the sense humans (and other primates) most depend on* in their daily lives
 - vision is not only used for *object recognition* but also to *guide movements*, and these two separate functions are mediated by at least two parallel and interacting pathways
 - visual processing starts from *V1*, the primary visual cortex (a.k.a. *striate cortex*) and follows different pathways through the *extrastriate visual areas*, a set of higher-order visual areas that are also organized as neural maps of the visual field
 - the two most known and major pathways are the *where pathway*, the one processing *where* the object is in the three-dimensional space, and the *what/how pathway*, the one processing *what* the object is and *how* it can be used to reach some goals
 - vision is often incorrectly compared to the operation of a camera, yet it is an active and creative process that involves more than just the information provided to the retina
 - visual perception involves an interaction between the retina, thalamic nuclei, and multiple areas of the cerebral cortex
 - it is based on a generative model that actively predicts and explains sensory inputs based on past experiences (the *Bayesian Brain* hypothesis)

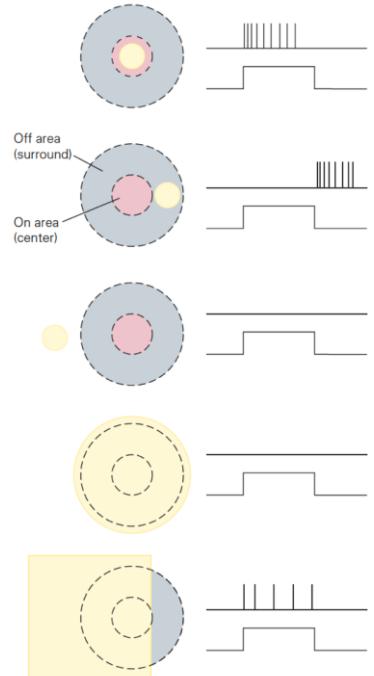
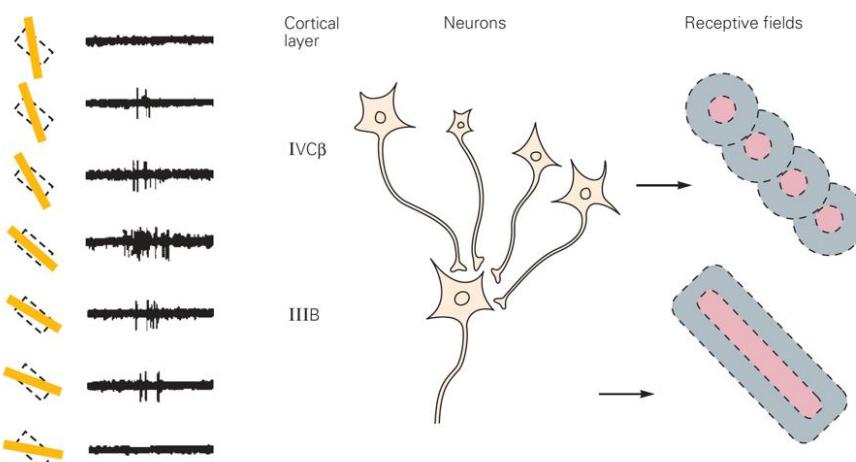


ANALYSIS OF VISUAL NEURONS

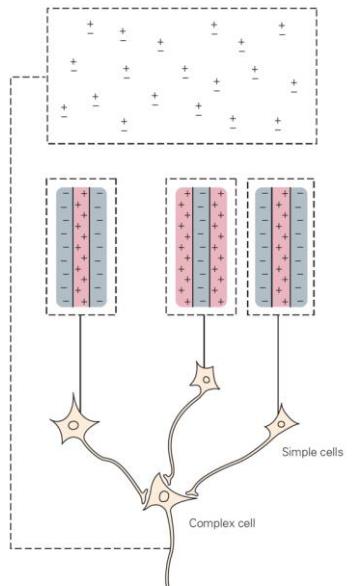
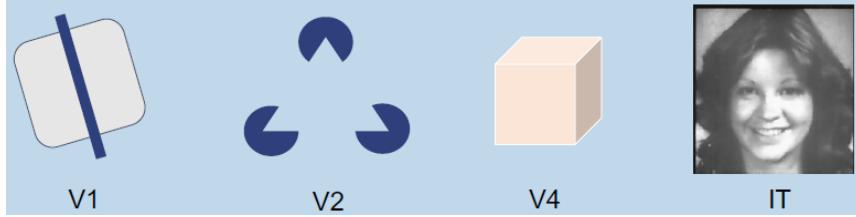
- **Single-Cell Recording** is a technique that allows recording signals from single neurons in the form of firing rates
 - This is an invasive procedure consisting in placing a metallic electrode inside the brain in order to record extracellularly change in electrical activity, namely the spikes (*peaks*) in the *action potential*
 - despite being so invasive, it is very used in experiments (with animals, generally primates or rats, only) thanks to its high spatial and temporal resolution differentiation between excitation and inhibition

- also, since spikes are all-or-none, most information is encoded in the brain as neuron firing rate, i.e., the number of *APs* in one second
- The primary goal of *single-cell recording experiments* is to determine what experimental manipulations produce a consistent change in the firing rate of an isolated neuron
 - differently from *EEG*, here we can focus on the activity **a single neuron** instead of the aggregated results of the activities of nearby neurons
- As **visual neurons** respond to stimuli in only a limited region of space, the so-called neuron's **receptive field (RF)**, *single-cell recording* can be exploited to identify that region at first and, eventually, to see how the neuron gets activated by stimuli presented in that region
 - the *RF* of a neuron can be identified by checking when it fires respectively to how a light stimulus is presented on a screen
 - *RFs* are different among neurons
 - each neuron has its own receptive field and each receptive field corresponds to one neuron only
 - a point in the space can be in many receptive fields, namely it is taken into consideration by many neurons
 - the set of points in the space that are in at least one receptive field form the field of view of the animal, which is almost 180 degrees, i.e. everything that is in front of the eyes
- With **Retinotopy** we refer to the fact that in early visual areas, neurons are organized in a topological way that resembles that one of the receptors in the eye
 - *Selective visual attention* can be seen as a cause that more cortical space is dedicated to the central part of vision, where the *RFs* are smaller and the visual system has the greatest spatial resolution
 - The amount of cortical area dedicated to inputs from within each degree of visual space, known as the **magnification factor**, varies with **eccentricity**, namely their position relative to the fovea
 - e.g. neurons connected to receptors in the fovea have a *receptive field of less than one degree*, while neurons connected to peripheral receptors have a much larger receptive field
 - also, the magnification factor varies with the position of neurons along the visual pathway, indeed *RFs* with the same eccentricity are relatively small at early levels and become progressively larger at later levels

- Neurons in different areas of the brain have **receptive fields of different shapes** and, because of that, they can respond to different patterns
 - *RFs* of retinal ganglion cells and LGN neurons, which are not selective for the orientations of lines or edges, are circular with a centre-surround organization
 - e.g. when the stimulus is presented in the peripheric area of one single receptive field, the neuron fires only when the stimulus disappears, while if the stimulus cover the entire receptive field, the neuron does not fire (still, all of its neighbours will fire because of a partial covering)
 - this mechanism is useful to encode changing in intensity of the stimulus between consecutive points in the space, indeed just neurons that perceive an edge will eventually fire
 - Instead, neurons in *V1* respond selectively to lines of particular orientations and they have been divided into two types by *Hubel and Weisel*
 - **simple cells**, in which receptive fields have **separate ON and OFF subregions**, namely they have a central region which is activating and a peripheral region which is inhibitory
 - differently from other cells, these ones have an *elongated receptive field* instead of a circular one, indeed they are receptive for orientation
 - the neuron fires when a stimulus, say a light, enters in the activating region only (with the specific orientation checked by the cell) or disappears from the inhibitory region, instead, if the stimulus appears in the inhibitory region only, in both the activating and inhibitory region or even outside the receptive field, the neuron will not fire
 - practically, these cells are in charge of looking for stationary edge-like patterns of a certain orientation in a certain region of the space

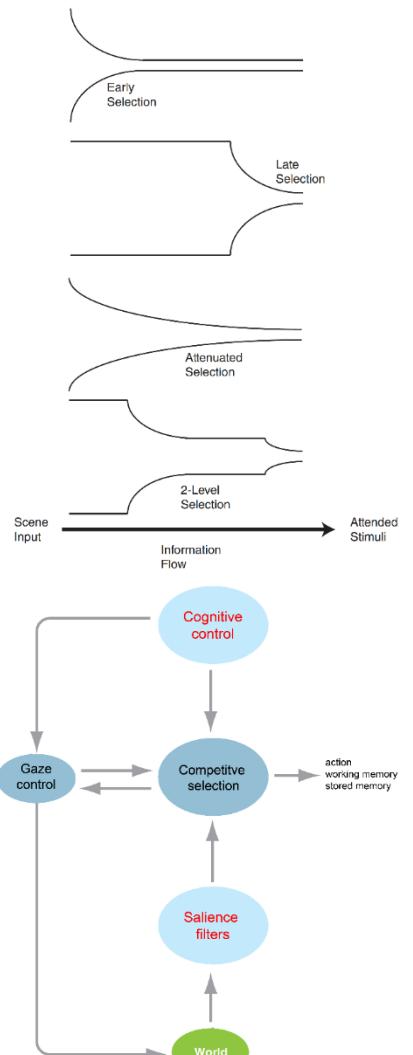


- *complex cell*, in which **ON and OFF regions are superimposed**
 - every location in the receptive field responds both to white and black bars, and cells respond continuously as a line or edge traverses the receptive field along an axis perpendicular to the receptive-field orientation
 - practically, these cells are in charge of looking for dynamic edge-like patterns, indeed they exploit the superimposition of single cells' regions in order to fire whenever a stimulus passes from the central/peripheral region of a simple cell to the central/peripheral region of the adjacent
- Anyway, in general, the complexity of neural processing increases along each cortical pathway
 - for instance, **V1** neurons respond to linear contrasts, **V2** neurons to illusory contours, **V4** neurons to the conjunction of elementary features, such as colour and shape, while **IT** neurons to complex stimuli, such as faces



VARIETIES OF VISUAL SELECTIVE ATTENTION

- In order to overcome its processing capacity, at a certain point (or *several* of them) between the input and the response, the brain must introduce a kind of selection in which each visual representation compete against each other to gain resources
 - This competition is biased towards information that is currently relevant to behaviour, indeed attended stimuli make demands on processing capacity, while unattended ones often do not
 - scientists agree on the fact that there is no attention mechanism during the early stage of visual processing, indeed photoreceptors in the retina do not filter any information, they just replicate data to the *Lateral Geniculate Nucleus* (in the thalamus), in which the first effects of selective attention can be seen, and are eventually improved in the visual cortex
 - four distinct kinds of bottlenecks have been proposed to be responsible for attentive behaviour, each one making a particular commitment to when attentional selection has its effect in the information flow
 - Attention in the visual field is not only a matter of cerebral resources but also a matter of visual resources, indeed visual processes try to direct the gaze towards specific points in the space in order to exploit the higher density of photoreceptors in the fovea for many possible and distinct reasons
 - moving the gaze towards next target
 - direct actions, e.g. reaching and grasping movements, at the selected object
 - allow entrance of the selected inputs into memory systems and perception
 - Finally, we can distinguish between a variety of visual selective attention, in which the selective processing comes in multiple forms
 - *top-down vs. bottom-up*, namely whether the attention is guided by voluntary mechanisms or automatic ones
 - *space-based vs. object-based*, namely whether the attention is guided by a space search or by specific characteristics of an object
- *covert* vs. *overt orienting*, namely whether the attention is expressed in a secret way (trying not to manifest it) or in an open way
- **Top-Down Attention** (or *endogenous attention*, or *voluntary attention*) is a selective process that can be engaged to select one thing over another as well as to follow a particular instructional set or general rule, and it is opposed to **Bottom-Up Attention** (or *exogenous attention*, or *automatic attention*), which is a selective process that allows novel or salient information happening in the environment to transiently interrupt the goal directed behaviour
 - Many different components play a role in *selective visual attention*, each one having particular roles and biases, for instance
 - the **Cognitive Control** is a *top-down process* that regulates the relative signal strengths of the neural representations based on current goal
 - e.g. if we want some strawberries and we open the fridge, then our attention will focus every time we find something red because we know strawberries to be red
 - the **Salience Filters** are a series of *bottom-up mechanisms* that automatically enhance responses to stimuli that are infrequent in space or time, or are of innate or learned biological significance, such as the seeking of food



- e.g. if we go to a wedding and one person is wearing a red suit, our attention will be focused on them because of their difference with respect to the environment, even though we were not expecting to find (or even to seek for) them
 - the **Gaze Control** is a mechanism to control the eye movement, which is affected by the cognitive control as, by seeking for something specific, we will have a certain perspective of the environment (i.e. the outer world) by moving our eyes towards specific areas
 - the **Competitive Selection** is the bottleneck process which, among each neural representation, allows the one with the highest signal strength for entry into working memory
- **Object-Based Attention** and **Space-Based Attention** can be studied by two different paradigms, respectively the *visual search paradigm* and the *cuing paradigm*
- In the visual search paradigm (*Treisman & Gelade, 1980*), the observer is presented with a display that can or cannot contain a target stimulus among a variable number of distractor stimuli, and the observers' task is to make a target present vs. absent decision as rapidly and accurately as possible
 - in the so-called *parallel search*, there is just one kind of distractor, vertical blue bars, which is very different from the target, the vertical red bar
 - observers scan the entire screen in parallel with a single gaze
 - while in the so-called *serial search*, there are two kind of distractors, vertical blue bars and horizontal red bars, one of them being quite similar to the target, which is the vertical red bar
 - observers scan the screen sequentially by blocks with multiple gazes where the attention is put on different portions of the screen
 - also, the scanning process depends on cultural background, as occidental people tend to scan the screen from left to right and from above to below
 - it has been shown that the efficiency of search decreases as the similarity between target and distractors increases, and increases as the similarity among distractors increases, indeed the most efficient searches are searches for a distinctive target amongst homogeneous distractors
 - In the cuing paradigm (*Posner, 1980*), a participant is asked to fixate the central cross of a screen until an arrow cue indicates where the target is more likely to appear, the cue is then followed by a target in either the correctly cued or the incorrectly cued location
 - generally, in these experiments the cue is valid in about 80% of the cases, while it is invalid in the remaining 20%.
 - this kind of paradigm can prove that the reaction time is way faster when the cue is valid than when the cue is invalid
- ## NEURAL CORRELATES OF VISUAL ATTENTION
- **Single-cell recording** is exploited during experiments in order to understand the neural correlates of visual attention, namely to understand when, how and why a certain neuron fires in response to certain visual stimuli
 - in order to do that, generally, a special stimulus is presented in the receptive field of the neuron (which has been previously calibrated) and the activity of that neuron is recorder through time
 - Studies on the **neural correlates of bottom-up attention** discovered that the response of single neurons is enhanced by feedback connections, indeed even though no particular pattern emerges in the receptive field of the neuron itself, it starts to fire after a small delay because a larger pattern has been found around it
 - *Lamme et al., 1995*: a square patch covering the entire receptive field was made to perceptually pop out by changing its orientation with respect to the orientation of the patch surrounding it
 - study shown that *V1* neurons gave the same response in both cases for the first 100ms, but after that time neurons significantly increased their firing rate in the cases in which the patch had a different orientation, meaning that it was able to notice a difference between that patch and the background thanks to recurrent feedback connections from other adjacent neurons
 - *Burrows et al., 2006*: in early visual areas (*V1* and *V4*), study reported that neurons exhibit enhanced responses to pop-out stimuli, i.e. those that differ from uniform surrounding items, relative to stimuli composed of a conjunction of surrounding features, placed inside the *RF* of a neuron
- Feature (parallel) search**

Conjunction (serial) search
- Reaction time (msec)**

Set size	Target present (msec)	Target absent (msec)
2	~450	~450
6	~500	~500
12	~550	~550

Reaction time (msec)

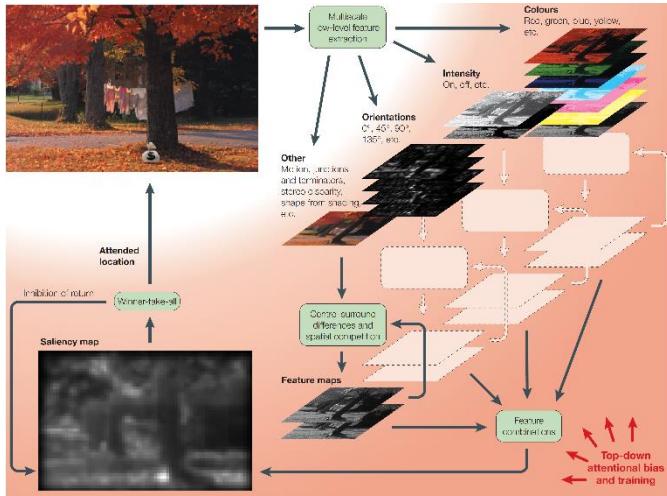
Set size	Target present (msec)	Target absent (msec)
2	~500	~500
6	~750	~750
12	~1000	~1000
- Valid cue**

Invalid cue
- Popout**

Conjunction
- figure surface**

background

- again, this is a proof that recurrent connections make it easy to find anomalies in the visual field, but just in case the anomaly is clearly different from the other elements in the scene



➤ *Gottlieb et al., 1998*: recording from the lateral intraparietal area of the monkey, it was found that neurons responded to visual stimuli only when these stimuli were made salient, but not otherwise

- e.g. a single stimulus can be salient because there is nothing else in the environment, while if more stimuli are present, then each stimulus becomes less salient

➤ As we already said, early stages of visual processing decompose the incoming visual input through an ensemble of feature-selective filtering processes

- it has been hypothesized (*Itti & Koch, 2001*) that the various feature maps feed into a unique **saliency map** (or *master map*), a 2D map whose activity topographically represents visual saliency, irrespective of the feature dimension that makes the location salient

- this saliency map biases attention to focus onto the most salient location and can provide an efficient control strategy for the deployment of attention on the basis of bottom-up cues

- As well, some studies on the **neural correlates of top-down visual attention** observed that selective visual attention increases visually driven firing rates of neurons encoding the attending stimulus, namely that if a stimulus is expected then neurons will fire more, and that the magnitude of attentional enhancement increases as one ascends the visual hierarchy, from early to late visual areas

➤ *McAdams & Maunsell, 1999*: monkeys were instructed to focus their attention either on one or the other hemifield where two stimuli, a *Gabor patch* and a distractor, respectively in and out the *RF* of a neuron, were presented on a screen

- as in many other experiments, the instruction of monkeys consisted in asking them to press a key whenever the patch changed orientation and rewarding them whenever they gave the correct answer

→ however, the answers given by the monkey are not part of the experiment results, but rather just a way to condition their behaviour
→ also, once finished the round of experiment in which the monkey should pay attention to the *Gabor patch*, it is possible to retrain the monkey to pay attention to the distractor in a fast by simply reward it when it correctly presses a key whenever the distractor changes colour

- results shown that when monkeys were trained to focus on the *Gabor patch* the neuron fired significantly more than when they were trained to focus the distractor in the other hemifield
- also, as neurons in *V1* and *V4* fire respectively to specific directions, it was noticed that a change in the orientation change the intensity of the activity of the neuron, still, the ratio between the intensity of firing when the stimulus was attended and when it was not attended was the same, regardless of the orientation of the patch
- in particular, the ratio was about 31% for neurons in *V4* and about 6% for neurons in *V1*, proving again that attention mechanisms grow proportionally to the hierarchy of visual areas, i.e. neurons in the extrastriate visual areas are way more selective than neurons in the primary visual area

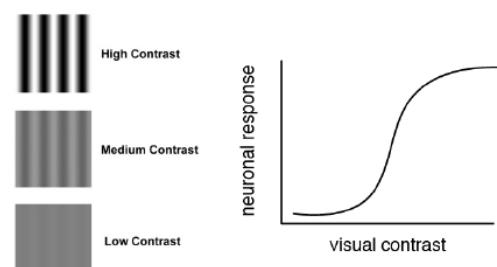
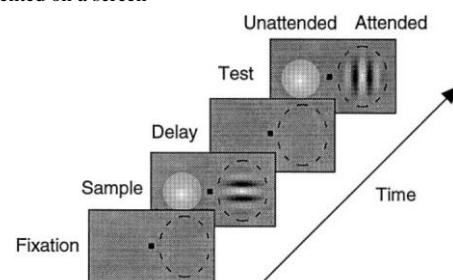
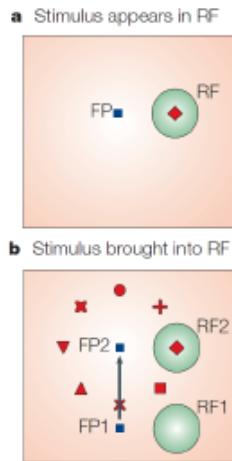
- Other than the orientation of the stimulus, another important role in the activation of visual neurons is played by the **contrast** of the objects in the receptive field and their **density**, indeed low-contrast stimuli are more difficult to perceive than high-contrast stimuli as well as dense stimuli are more difficult than sparse one, because whenever the receptive field has to deal with multiple stimuli appearing in the same area, sometimes it is not so easy to distinguish between them if their distributions overlap

➤ In the visual system, a non-attentional, i.e. *bottom-up*, enhancement effect can be achieved by changing stimulus contrast, indeed visual neurons typically produce increasing responses as a function of stimulus contrast in the form of an H-ratio function (similar to a sigmoid)

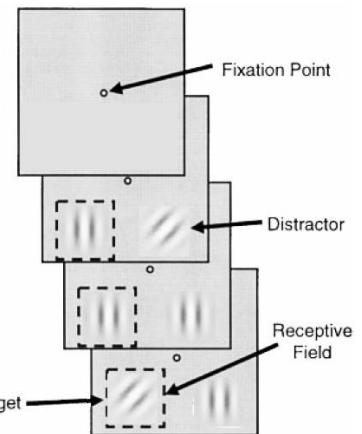
- the effect of *top-down attention* in such a model can be explained by the following logistic formula, proposed by *Martinez-Trujillo & Tre*, taking into account the maximal response R_{max} of the neuron and the contrast C^n in which the response is at 50% between the minimal and the maximal

$$response = \frac{R_{max} \cdot C^n}{C^n + C_{50}^n} + M$$

- still, being n and M two fixed parameters and C^n is the input of the function, *top-down attention* could modulate the response either by *increasing the maximal response R_{max}* or by *decreasing the peri-threshold contrast value C_{50}^n* , giving rise to two different, equally plausible models, respectively called **response gain model** and **contrast gain model**



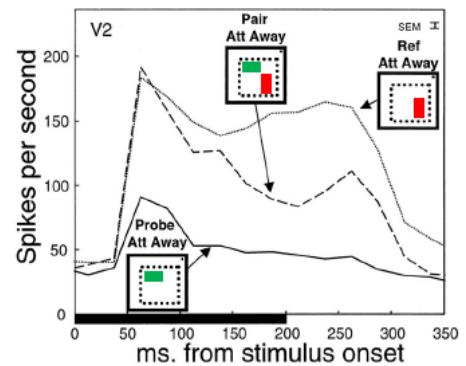
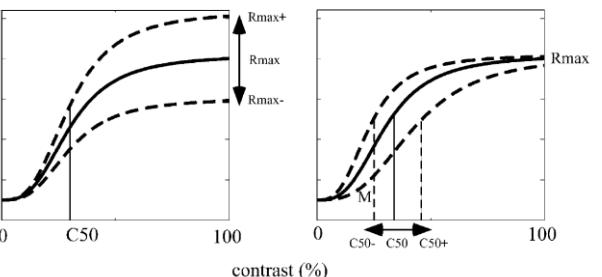
- *Reynolds et al., 2000*: as in McAdams and Maunsells' 1999 experiment, monkeys were trained to pay attention either to a target stimulus inside the RF ("attend RF" block of the experimental procedure) or to a distractor in the other hemifield ("attend away" block of the experimental procedure), still, this time, instead of orientation it was changed the luminance contrast of each stimulus from a set of five contrasts that spanned the dynamic range of each neuron's RF
 - results show that responses, expressed in terms of spikes per second, were higher in the *attention* block with respect to the *non-attention* block mainly for low contrasts, while as stimulus contrast increased, the effects of attention on the neuronal response decreased
 - this can be regarded as a proof that attention causes an increase in V4 neurons' sensitivity but without a substantial increase in the response to high-contrast stimuli, thus neurons are more prone to follow the *contrast gain model* rather than the *response gain model*
 - this is also quite intuitive, indeed, as high contrast stimuli are easily visible whether there is or not a focus on them, there is no need to increase the firing rate, while for low contrast stimuli this turns out to be a great behavioural skill because we can consciously allow more brain resources to detect edges and, in general, shapes, in low contrast stimuli that we would not be able to detect just with *bottom-up* methods
- As well as contrast, also the *density* of the stimuli presented in the same receptive field is hard to manage with *bottom-up techniques* only
 - for instance, let us consider a neuron responding to red stimuli, then it will not be activated by, say, a green stimulus, but if both of them are presented then the neuron will respond with an averaged signal
 - as we can see in the picture, even the green stimulus initially creates some activity in the neuron, but that is just because the stimulus popped out from nowhere and, thus, activated a response which is then deactivated
 - however, this averaged response is difficult to interpret by adjacent neurons, as it could mean either that multiple stimuli are presented within the receptive field or that, for instance, a single, brownish stimulus is presented
- *Moran & Desimone, 1985*: the previously presented multiple stimulus consisting in a green horizontal bar and a red vertical bar is subjected to monkeys that are instructed to focus their attention either to one or the other bar, so that even though both the stimuli are into the receptive field of the same V4 neuron, monkeys will give more importance to one of them only
 - results show that, when the monkey was focusing its attention on the red bar, the neuron got a significantly stronger activation than when it was focusing its attention on the green one, with the spikes plots being very similar to those obtained undergoing the red stimulus only or the green stimulus only
 - this can be regarded as a proof that *top-down attention* is able to *enhance the visual system's spatial resolution* (or *acuity*) in order to better discriminate two nearby points in space



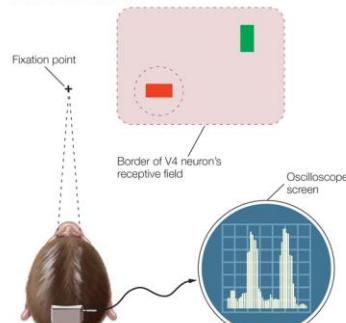
A response gain model



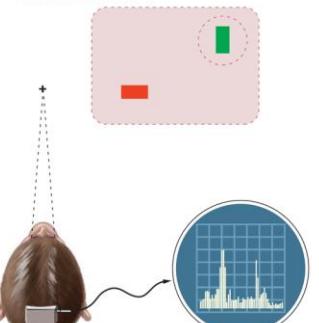
B contrast gain model



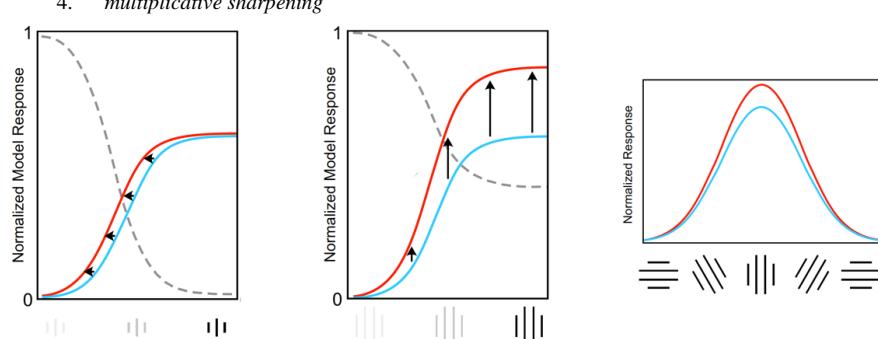
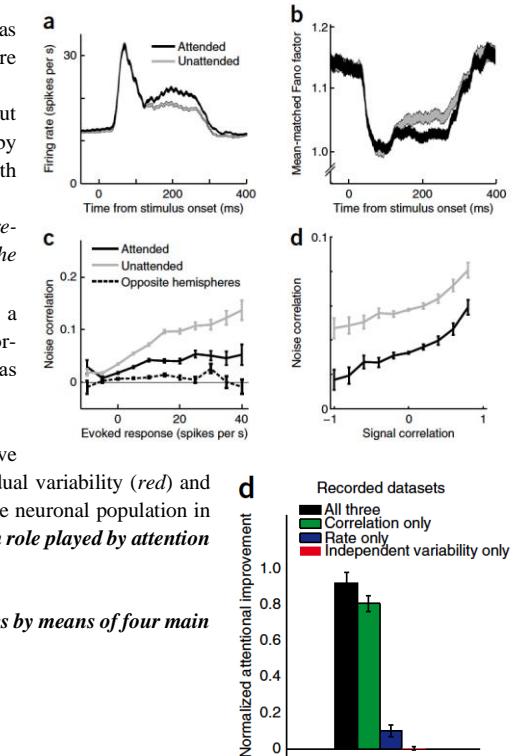
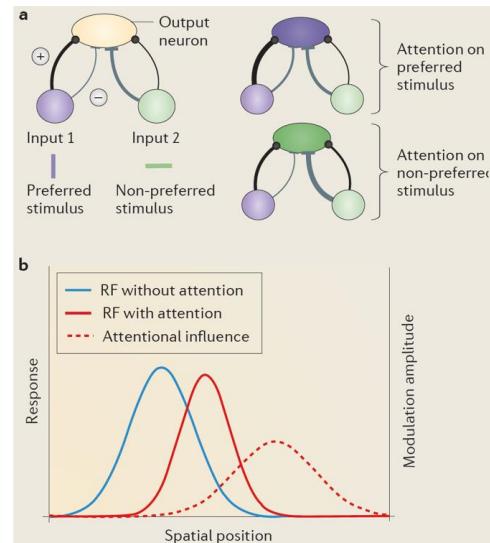
Effective stimulus attended



Ineffective stimulus attended



- e.g. this can happen at a neural level by either strengthening or weakening the connections between some input neurons (encoding, for instance, the fact that a stimulus is green or red) and the output neuron, namely the one taken into consideration for the experiment
- Another effect of attention at neural level is to **reduce correlation between neurons monitoring the same areas of the environment** in order to decrease the amount of noise shared between them and perform a better aggregation of results
 - Indeed, in order to better represent the environment in which it moves, the brain aggregates the results of each neuron coding for a particular aspect of a particular point in the space, and the results of this aggregation aim at reducing the noisy signal that can interfere with a correct representation of the environment
 - for a single point/area in the space there are many visual neurons that are monitoring that and extracting features from that point/space, still, if the noise in individual neurons is not independent, then the shared variability can never be averaged out, leading to a more variable (and less accurate) estimate of the mean activity in the total population of neurons
 - one of the mechanisms of attention, indeed, is to limit the correlation between those neurons and let them make their own processing without interfering with the other ones, so that in the final aggregation noisy signals could annihilate themselves
 - Cohen & Maunsell, 2009: a population of nearby neurons in V4 was recorded in monkey brains using two 6×8 arrays of microelectrodes, which allowed to investigate the effect of attention on correlated variability on both hemispheres, while monkeys were performing an orientation change-detection task in which two Gabor stimuli were flashed on and off and the monkey's task was to detect a change in the orientation of either stimulus
 - as in the other experiments, the attention of the monkey was previously manipulated in blocks by cueing the monkey as to which stimulus was more likely to change, with the cue being valid on 80% of trials
 - results showed that, as already known, attention increased V4 firing rates, but also reduced the trial-to-trial variability of individual neurons, as indicated by a drop in the *Fano factor*, i.e. the ratio of the variance of the firing rates with respect to the mean
 - however, the most important result was that attention *decreased noise correlation*, namely the correlation between the *variability or fluctuation of the responses of pairs of neurons*, in each trial
 - this value represents how much variability (or noise) is shared by a group of neurons, and for pairs of neurons in the same hemisphere, correlation was lower when the stimulus in the neurons' receptive field was attended than when it was unattended
 - finally, a plot bar was produced to better understand, respectively, the relative importance of increasing single neuron discharge (*blue*), reducing individual variability (*red*) and reducing correlated noise (*green*) in increasing the sensitivity of the whole neuronal population in the attended versus unattended condition, eventually showing that **the main role played by attention is to reduce correlated variability**



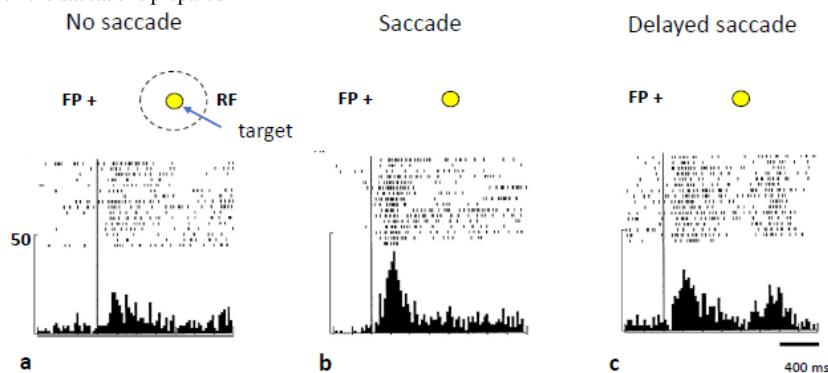
COVERT vs. OVERT VISUAL ATTENTION

- Gaze direction and attention are often spatially aligned, however it is also possible to attend to objects of interest in the visual scene without shifting our gaze, and we refer to these cases as *overt* and *covert attention* respectively

- One thing to take in mind is that, whenever the gaze is moved in a fast way from one point to the other, something called a *saccade*, the attention is always shifted along the direction of the eye, but the opposite does not hold, as it is possible to *shift the attention without moving the gaze*
 - the possibility to shift the attention while maintaining a fixed eye position is a behavioural mechanism used by animals to monitor a certain resource (e.g. food, babies, ...) in a hidden way
- Covert attention is the form of spatial attention most often studied in vision neuroscience, indeed, in the majority of the experiments, animals are required to maintain their gaze in the fixation point while moving their attention
 - this is simply because, if the gaze is moved together with the attention, then the *RF* of the recorder neuron will move as well, being the coordinates of the *RFs* expressed in terms of relative position with respect to the fovea

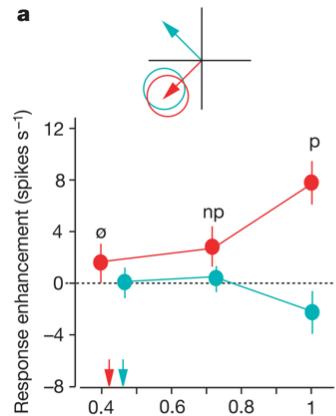


- Relationship between *saccade preparation* and *spatial attention* has been proved many times in different experiments by analysing the way the *Frontal Eye Field (FEF)*, a region of the brain in the prefrontal cortex, is able to generate saccades
 - *FEF* neurons receive projections from most visual areas and, if stimulated enough, generate a saccadic response towards *specific directions*, however, they also have feedback projections to the visual cortex that suggest a pathway by which saccade related signals can influence visual processing
 - considering that, due to physical limitations (i.e. the inner inertia of the eyes), a saccade takes *200ms* to be performed, the presence of feedback connections also suggest a strong correlation between the intensity of firing in *FEF* neurons and early visual areas neurons during the presaccadic time, as known as *presaccadic visual enhancement*, or rather this precise fact that visual activity in a number of brain regions is enhanced immediately before an animal targets a stimulus with a saccadic eye movement
 - this was first observed among neurons of the superior colliculus, but later studies demonstrated the effect in the *FEF*, parietal cortex and several extra striate visual areas
 - *Moore & Fallah, 2001*: in three different experimental blocks, monkeys were instructed to maintain their gaze on a given fixation point (*FP+*) until a stimulus was presented in the receptive field of a recorder neuron, and then respond by continuing to maintain the gaze on the *FP* (*no saccade* block), instantly moving the gaze towards the stimulus (*saccade* block) or move the gaze towards the stimulus after a small amount of time (*delayed saccade* block) respectively
 - differently from the previous experiments, here the monkey is allowed to perform the saccade (i.e. move the gaze), indeed we are just interested in the activity of the neuron between the stimulus and the (eventual) saccade, namely the *200ms* in which the saccade is prepared



- as we can see, when the monkey was trained to move the gaze towards that specific area in which the stimulus would appear, namely the monkey's *top-down attention* was manipulated in order to get a faster response, the neuron shown a higher activation with respect to the *no saccade* condition, as if the monkey was able to ignore the outer stimulus in order to concentrate on the fixation point when asked to
- Finally, the activity of *FEF* neurons and the role of attention in visual areas was further studied to show not only a correlation but a causal link between the two
 - We know that each *FEF* neuron produce the saccade towards a specific direction (e.g. upper-right, lower-left, ...), which is referred to as its *motor receptive field*, thus we can generate saccades towards a specific point in the space in monkeys by electrically stimulating the correct *FEF* neuron with a microelectrode
 - the same thing could be done in humans, with minor effects, using *TMS*
 - the peri-threshold current to generate a saccade in a monkey is about $50\mu A$, meaning that if we stimulate the neuron with more than $50\mu A$ we will certainly see the monkey moving its gaze towards the selected direction, while if we stimulate it with less than $50\mu A$ the monkey will maintain its gaze

- still, a sub-threshold stimulation must have a sort of effect, as it generates a chain of action potentials in nearby neurons
- the hypothesis is that sub-threshold stimulations do not actually perform the saccade but, instead, *prepare* the brain to perform it, namely it increases the attention of the brain towards the area in which the saccade will point if performed
- *Moore & Armstrong, 2003:* two microelectrodes are placed in the brain of a monkey, one in the *frontal eye field* to stimulate a certain neuron with a sub-threshold current, and one in *V4* to record its activity when a stimulus is presented inside its receptive field
 - actually, two different neurons in the *frontal eye field* were stimulated in two different blocks, the first one evoking a saccade in the direction of the receptive field of the recorded *V4* neuron, and the other one in a direction which is perpendicular with respect to that receptive field
 - results show that while the response of the *V4* neuron had a similar trend both in the *0 condition* (no stimulus) and the *np condition* (non-preferred stimulus) either when the controlled *FEF* neuron was the one evoking the saccade in the same or the perpendicular direction, it shows a significant shift in response during the *p condition* (preferred stimulus), where the stimulation of the correctly directed *FEF* neuron enhanced the activity while the stimulation of the perpendicularly directed *FEF* neuron diminished it
 - results suggest that the gain of visual signals is modified according to the strength of spatially corresponding eye movement commands, namely that sub-threshold stimulations effectively modulate the attention in early visual areas by means of feedback connections and, indeed, prepare the brain to perform the saccadic movement in the corresponding direction



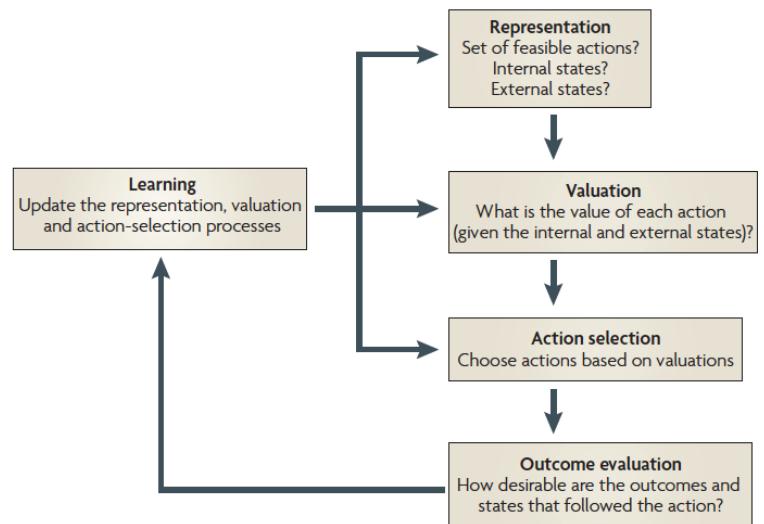
PERCEPTUAL DECISION MAKING

- A **decision** is a *deliberative process* that results in the commitment to a categorical proposition (i.e., selection of a course of action) based on sensory information about the environment and the organism's internal state
 - Organisms release cached (i.e., *learned*) action at appropriate occasions/times, then, once learned, these actions become stereotyped and inflexible
 - During the *deliberation*, namely a *careful consideration* of the possible outcomes, the agent searches through potential possibilities based on a hypothesized model of how the world works and evaluates them in order to, eventually, make the best decisions
 - the *deliberation* depends on three steps
 1. determining what those possibilities are
 2. evaluating the outcomes
 3. selecting which action to take
 - the final *decision* involves the following elements
 1. prior knowledge, i.e. the memory of the agent
 2. sensory evidence, i.e. the current state of the agent
 3. anticipated value/cost, i.e. the deliberation process
 4. action, i.e. the final choice
- We can distinguish between two main types of **Decision Making (DM)**
 1. *Perceptual Decision Making (PDM)*, or *Evidence-Based Decision Making*, in which the agent selects action *A* or *B* depending on the strength of the external signals, namely how much those signals are coherent or noisy
 - the sensory information is noisy and can be not accurate enough to perform a one-hundred percent correct decision, thus the agent should take in mind the uncertainty of the perceptual information when making the final choice
 - in this case, the source of uncertainty is the stimulus itself, indeed we do not take into consideration the outcomes of each choice
 2. *Value-Based Decision Making (VBDM)*, or *Economic Decision Making*, in which the agent selects action *A* or *B* depending on its internal goals or preference, namely it associates a sort of anticipated score to each action
 - here, the sensory information is clear, and what is uncertain is the value associated to each alternative, thus the decision must be taking by assigning hypothetical scores to each alternative and choose the better one basing on the predicted values
 - in this case, the source of uncertainty is the value associated to each action, which are learned basing on previous experiences by evaluating how much previous prediction differed from the real outcomes

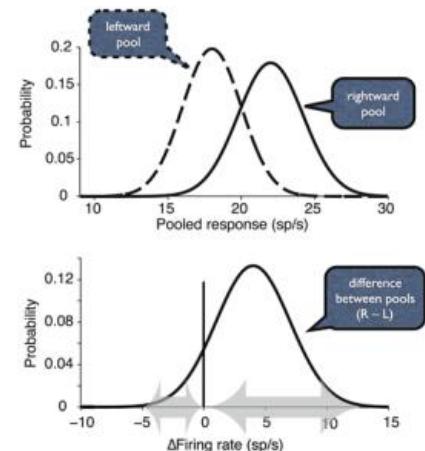
THEORETICAL MODELS FOR PERCEPTUAL DECISION MAKING

- **PDM** can be conceived as a process of *statistical inference* from the noisy representation of evidences (i.e., stimuli) to a categorical choice, or rather, it is the process of trying to understand the state of environment given the noisy data provided by the sensory systems

- As already said, in *PDM* the decision is not related to an individual's goal, but simply to compute the most correct hypothesis among the possible ones (h_1, \dots, h_n) representing the state of the world
 - generally, $n = 2$, for instance one of the possible choices to be made can be to understand either if a stimulus, say a ball, is moving towards us or in the opposite direction
 - it is just in a second moment, i.e. once understood the direction of the ball, that *VBDM* can use this piece of information to decide whether to move left or right in order to avoid the ball hitting our face

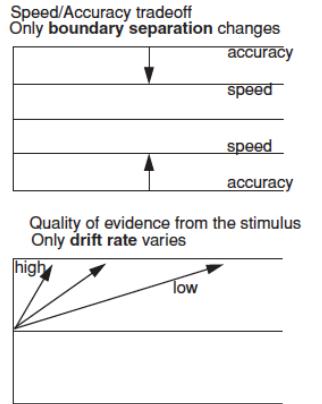
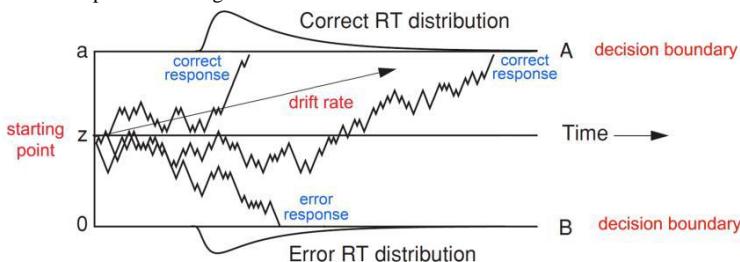


- This statistical inference takes advantage of a so-called **Decision Variable (DV)**, which takes care of mapping the evidences into the final choice
 - A *Decision Variable (DV)* represents the accumulation of all sources of priors, evidences, and values into a quantity that is interpreted by the decision rule to produce a choice
 - the *prior*, $P(h_i)$, is the probability associated, before obtaining any evidence about it, to the fact that a certain h_i is true
 - e.g. it can be the predicted probability of seeing a particular stimulus or receiving a particular reward on the upcoming trial
 - the *evidence*, e , refers to information that bears on whether to commit to a particular hypothesis, which turns out to be useful when it can be interpreted in the context of conditional probabilities
 - indeed $P(e | h_i)$ represents the likelihood function describing the values reachable by e when h_i is true
 - the most plausible representation of the world is that one having the maximal likelihood, namely $\max_i \{ P(e | h_i) \}$
 - the *value*, v , is a subjective cost that is attributed to each of the potential outcomes of a decision process
 - it can be manipulated by external agents by giving explicit feedback or monetary rewards to human subjects rather than preferred food or drink to nonhuman subjects
 - also, value can reflect more implicit factors such as the costs associated with wasted time, effort, and resources
 - Moreover, the *DV* is not tied to the single moment in which the stimulus appears but, instead, it spans the time from the first pieces of relevant information until the final choice is made
 - also, unlike the choice, which is indeed discrete, the *DV* should be thought of as an analogue quantity that gets progressively fine-tuned in the brain
- One theory through which we can model *PDM* is **Signal Detection Theory (SDT)**, where hypotheses are described according to a certain *probability distribution*, and the objective of the agent is not to determine whether the parameters describing these distributions are different but rather to decide which of the states gave rise to the observation e
 - e , which is the observation derived from the senses, is caused by a stimulus or a state controlled by the experimenter, e.g. an object moving up or down, and might be measured in terms of the spikes from a neuron or pool of neurons, or a derived quantity such as the difference between spike rates of two pools
 - if e is informative enough, then its magnitude differs under these states, still, it is generally corrupted by noise, thus it can be identified by a random variable described by a distribution whose parameters are set by the hypotheses
 - The main problem of *SDT* is that it is a static theory, indeed there is no natural explanation for the amount of time it takes to complete a decision, while as said before the *DV* is a concept that varies in time from the beginning of the stimulus until the final choice



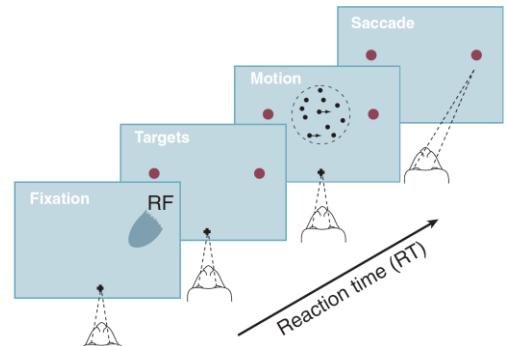
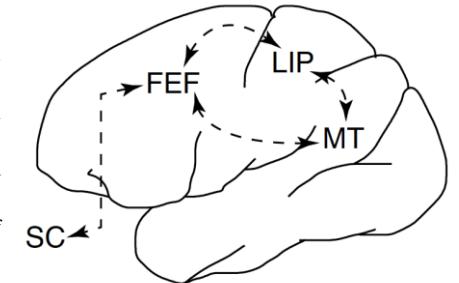
- To overcome the limits of *SDT*, we can model *PDM* through **Sequential Sampling Models (SSM)**, in which the time variable is taken into account, indeed we consider decisions to be made according to a batch of accumulated noisy evidences about the stimulus, the so-called *multiple sampling*, which is progressively integrated and revisited as new sensory evidences are gathered
 - According to *SSM*, after each acquisition, a *DV* is calculated from the evidences obtained up to that point, then a decision could be to wait and gather more evidences or to terminate the process with commitment wither to h_1 or h_2
 - in *random walk models*, the information is accumulated as a single total, where information in favour of one response is evidence against the other
 - in *race models*, information favouring the two responses are accumulated and processed separately

- In general, decisions are made by accumulating information over time from a starting point toward one of two response criteria (or *boundaries*), and this decisional process can be modulated according to two parameters
 1. the **Drift Rate**, i.e. the rate of accumulation of information, which is determined by the quality of the information extracted from the stimulus
 - if the information quality is poor, namely it is affected by a lot of noise, then the rate of accumulation is slower, and errors are more likely
 2. the **Boundary Separation**, i.e. the amount of information needed for a response, which is an arbitrary value used to calibrate the better *trade-off* between speed and accuracy of the response
 - while the drift rate is related to the environment and the quality of the signals it sends, *boundary separation is decided by the agent itself*
 - practically, this value decides how much coherent information do we need to choose one hypothesis and not the other one, thus the lower the boundary, the faster the response
 - this boundary can be equidistant from the starting point (z) or not, and in this second case we say that there is a *bias* which prefers one hypothesis over the other, probably due to some kind of prior knowledge



NEURAL CORRELATES OF PERCEPTUAL DECISION MAKING

- Trying to search for neural correlates of *PDM* means to seeking for the place in the brain where the *Decision Variable* gets progressively constructed
 - We need to find one or more areas in the brain involved in both motor and sensory stimulation and that deals with temporally prolonged stimuli and responses
 - the literature has mainly focused on parts of the brain involved in the selection and preparation of eye movements (saccades, *SC*), namely
 - *MT*, the *Middle Temporal area* (a.k.a. *V5*), primarily involved in the detection of motion
 - *LIP*, the *Lateral Intra-Parietal area*, primarily involved in eye movement
 - *FEF*, the *Frontal Eye Field*, also involved in eye movement
 - In order to study animals' neural responses and find neural correlates of the *DV*, the main paradigms exploits the so-called **Ran-dom-Dot Motion (RDM)** direction discrimination task, in which an ensemble of points moves randomly towards two directions, and the global movement is controlled by the experimenter which varies the percentage of coherently moving dots
 - the direction decision is typically indicated by the animal with an eye movement, and obviously the more the coherence between the dot direction, the easier (and faster) the correct response
 - the *RDM* paradigm has various advantages, indeed
 - the time needed to make the decision is particularly long for perceptual tasks is typically of various hundreds of milliseconds, allowing to study how the decision process unfolds in time
 - there is a strong link between the direction decision and a particular course of action, i.e. the eye-movement response, and this link enables investigators to treat the decision as a problem of movement selection
 - Britten et al., 1992: monkeys are undergone an *RDM* discrimination task while recording the activity of one of their *MT* neurons which is selective for stimuli moving rightward, and once the stimulus is vanished, monkeys are trained to perform a saccade either at the left or right part of the screen depending on the dots direction
 - We may expect the neuron to have a strong activity when the dots are coherently moving rightward (the so-called *preferred direction*), an almost flat activity when they are moving leftward (the so-called *null direction*) and an averaged activity when the coherence of the movement is low, indeed, what has been observed is that depending on the coherence of the dots the neuron can respond with a different activity which, even though being quite stochastic, can be easily modelled as two different gaussian curves

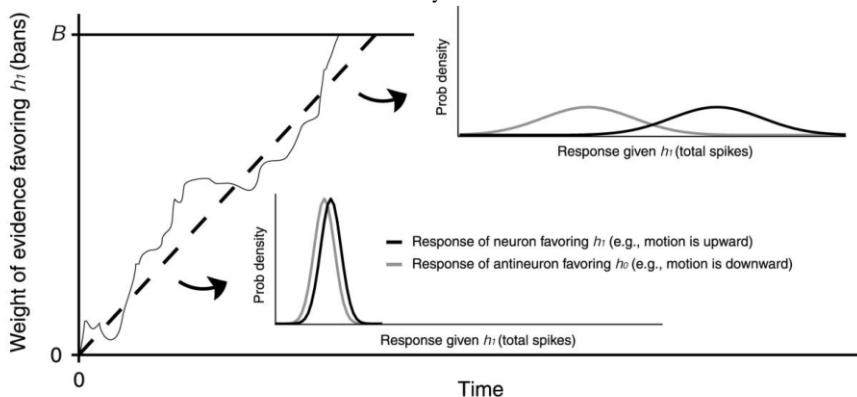


- in particular, in the picture on the side, we see that solid bars indicate the responses of the neuron (expressed as the total number of spikes during the presentation of the stimulus) when the stimulus is going leftward while the hatched bars indicate the responses of the neuron while the stimulus is going rightward
- as predictable, when the coherence of the movement is high, the neuron effectively has a weak activity for leftward stimuli and a strong activity for rightward stimuli, while when the coherence is low the response is not so clear, resulting in less separated probability distributions

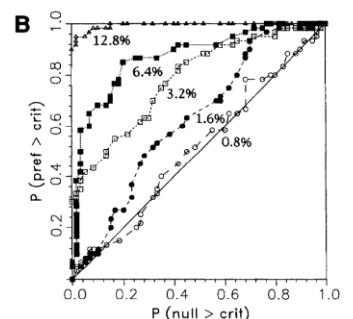
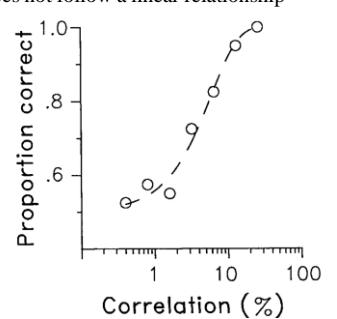
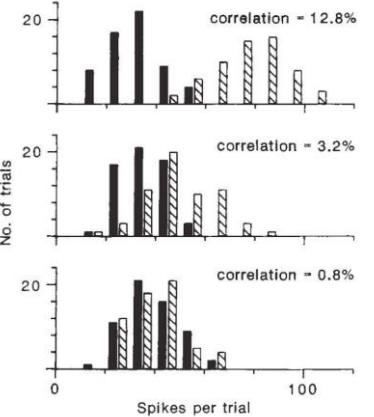
- Theoretically, we can see the distributions of these two responses as two *Probability Density Functions (PDFs)* that, given the evidence e , respectively represent the conditional probabilities $P(h_1|e)$ and $P(h_2|e)$, where h_1 and h_2 are the two possible discriminative hypotheses according to which the dots are moving either rightward or leftward
- once having the two *PDFs*, the final decision could be made by computing the so-called *Likelihood Ratio (LR)*, namely the ratio between the two distributions, and see whether this value is higher or lower than one
 - still, in order to compute the *LR*, the brain would need to know the information represented by the *PDFs*, thus the approach used by the brain is to **use the difference in spikes between two neurons** (or *pool of neurons*), respectively called *neuron* and *anti-neuron*, in which the first one is selective for the hypothesis h_1 and the other one is selective for the hypothesis h_2
 - called x the response, in terms of number of spikes, of the *MT* neuron selective for rightward movements and y the response of its anti-neuron, as well in *MT*, selective for leftward movements, then the so-called **total weight of evidence at time $t = k$** can be computed using the formula

$$T(k) = \int_0^k (x(t) - y(t)) dt$$

- this formula shows how evidences gets accumulated and integrated as more time goes on, and the final decision gets made as soon as this value reaches the boundary B

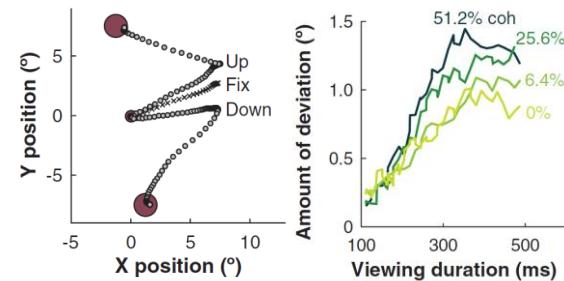
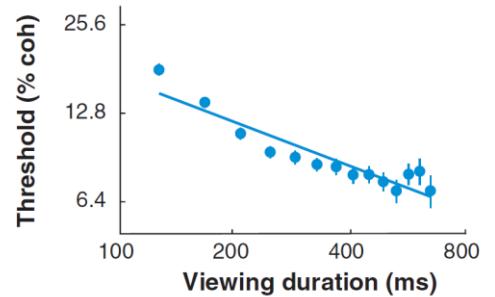
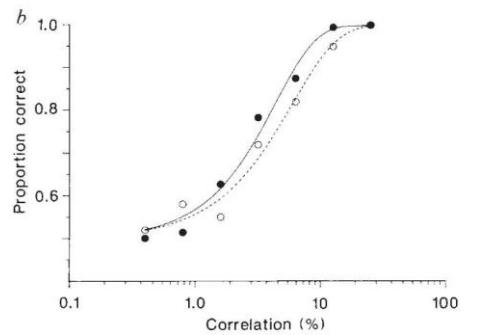


- Once understood how things work from a neural point of view, it is possible to focus on the macroscopic monkeys' responses, and see that their accuracy with respect to the discrimination task can be represented as a sigmoidal curve known as *psychometric function*, meaning that the ability to discriminate between leftward and rightward movements does not follow a linear relationship with the accuracy but, on the contrary, has a higher variation for median coherences until a plateau is reached both too weak or too strong signals
- when there is no correlation between points, namely the stimulus has almost no coherence (it is a pure random movement), then the accuracy is 50% as the monkey will respond randomly and guess the right answer in half of the cases, while when we increase the correlation the accuracy increases as well until it reaches a plateau after which the accuracy is always maximal
 - eventually, we can correlate this macroscopic behaviour of the monkey with the microscopic one, namely its neural activity, by looking at the so-called *ROC (Receiver Operating Characteristic) curves* obtained from the analysis of the *MT* neuron analysis
 - for each level coherence we have a curve, and we can build the so-called *neurometric function* by computing the normalized area under the respective curve for each level of coherence
 - as the *neurometric function* and the *psychometric function* have consistent values, we can conclude that the decision whether to move the gaze leftward or rightward is (almost) completely made by the pool of neurons whose activity was recorded



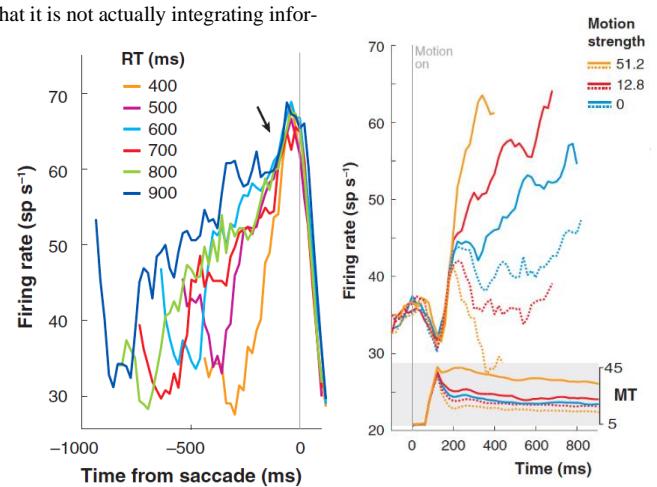
- Gold & Shadlen, 2000: the same kind of RDM discrimination task, this time with dots moving either up or down, is presented to monkeys, still here there is no recoding in MT but, instead, an *electrical stimulation* in a FEF neuron used to interrupt the task by evoking a saccade towards right before the monkey itself is able to move the gaze up or down in order to give its response

- If we let monkeys to finish the task and give their response by naturally move the gaze wither up or down, they will perform a decision in a time which is inversely proportional to the square root of the time, coherently to what is predicted by the *Sequential Sampling Models* theory
- this somehow suggest that, as we said before, the brain progressively updates the *Decision Variable* until it reaches a given threshold, still it is not known if there is a central processor which takes in charge the computation of the variable and, finally, sends the subsequent signals (e.g., in this case, to move the gaze up or down), or if each part of the brain is always aware of the total amount of information incoming
- By generating a saccade before the monkey would naturally move its gaze, we can notice that, even though the stimulated saccade should point in a certain area of the space, it would be directed slightly (but significantly) more upwards or downwards depending on the direction of the dots, meaning that in FEF there is a little amount of charge already present in the pool of neurons, which is exactly the neural correlate of the *Decision Variable*
 - this experiment proves that not only the area involved in the computation (MT) but also those involved in the action execution (FEF) actually computes the DV, meaning that the flow of information between sensory neurons and motor structures is more or less continuous
 - e.g., if we are deciding whether to perform an action or not, there is not a moment in which the decision is taken another one in which is propagated to the motor areas, but instead the motor areas gets preactivated and take an active part in the computation
- Finally, the last chart shows the correlation between the amount of deviation of the gaze respectively to the standard fixation point (expressed in *degrees*) and the time passed from the presentation of the stimulus until the evocation of the saccade for each coherence in the RDM task
 - this chart clearly shows how the information gets progressively integrated until the convergence towards a boundary, indeed to higher the amounts of time correspond a greater variation, independently from the coherence of the dots

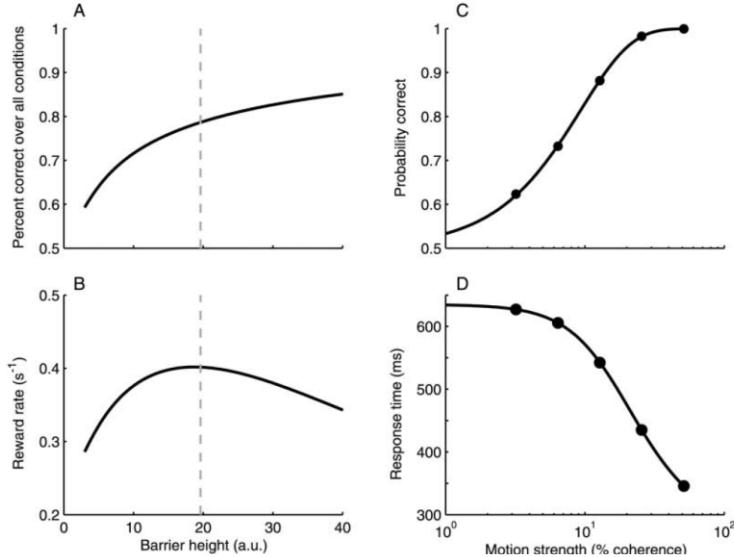


- Roitman & Shadlen, 2002: here, while recording the activity of one of their neurons in the LIP area, monkeys are subjected to a slight variation of the RDM task, namely a *Reaction-Time (RT)* variation in which they are trained to respond as soon as possible to the stimulus, indeed, given the same accuracy, a monkey that gives the response in a smaller amount of time would receiver a better reward

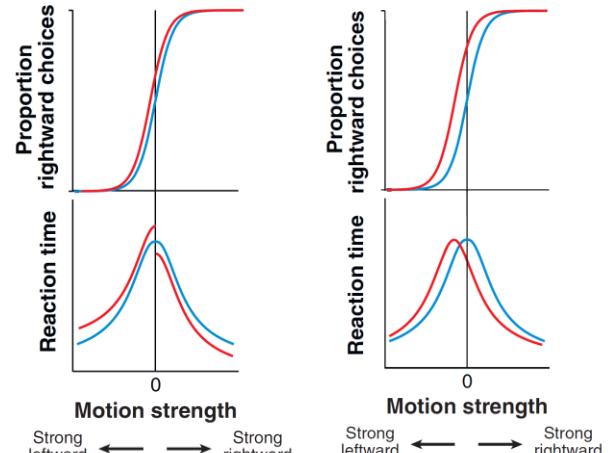
- By studying the firing rates of the LIP neuron after the presentation of the stimulus, we can see that, accordingly to the previous experiments and to the *Sequential Sampling Models*, the activity is stronger when the dots motion is more coherent and weaker when is less coherent, still, in general, the trend resembles a *random walk* towards a threshold representing the level of evidence required to reach a decision, at which point the decision process terminates
 - the initial peak is probably due to the fact that each neuron, independently from the things it is selective for, naturally respond to salient stimuli because of *bottom-up* selective attention mechanisms
 - besides that, we can see from the recordings of the MT neuron that it is not actually integrating information but, instead, its firing rates remain steady throughout time and are respectively high or low depending on how strong is the signal, meaning that MT does not computing the decision variable but rather it is simply a vehicle to propagate the evidence from the retina to LIP
- Also, if we consider instead the firing rates of the neuron before the monkey performs the saccade to explicit its choice, we can notice how, independently from the total reaction time and the trend of the random walk, the highest peak reached is that of *70 spikes per second*, after which the activity ceases
 - the value of *70 spikes per second* represents the barrier after which the monkeys got convinced enough by the evidences to give an answer
 - the actual the saccade is performed *70ms* after the peak is reached, meaning that the LIP takes exactly that time to perform the eye movement but, again, the preparation took place directly inside the motor area and not in a separate headquarter



- Finally, if we look at the accuracy of the monkeys and their average reaction times, we could notice that not only the former, but also the latter show a sigmoidal trend (in particular, an inverse sigmoid for the reaction times), meaning that the monkey is trying to balance its accuracy with the time spent to reach it in order to maximize the reward received



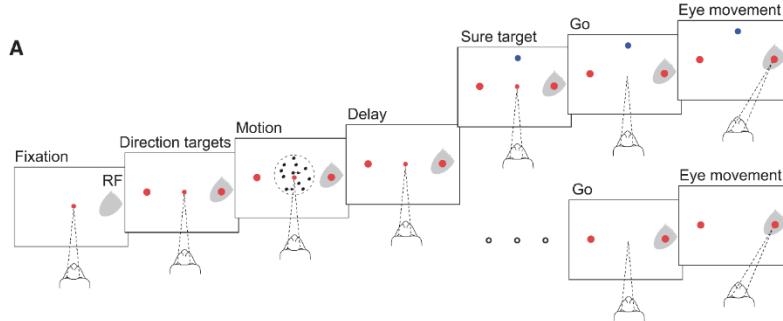
- if we consider the *rate of reward*, r , as a function depending both to the probability of a correct response and the average time per trial, we can see that, unlike the *overall performance*, it is a **non-monotonic function** whose maximum is exactly the **barrier height B**
 - in practice, the monkey does not care about its accuracy, but rather about the rewards it gets, indeed it sets the barrier taking in mind that if it is too low, then there are too many errors, which do not yield a reward, but if it is too high, then time is wasted and the reward is poor
 - however, how the brain might go about adjusting the level of the barrier, B, is an open question, but many thinks that this could be accomplished by a process of trial and-error, in which the barrier is raised and lowered until the maximum rate of reward is achieved
- Hanks *et al.*, 2006: the usual *RT-RDM* discrimination task is paired with an electrical micro-stimulation either of a rightward *MT* neuron or a right-choice *LIP* neuron to further establish the causal roles of the two areas of the brain when it comes to perceptual decisions
 - Micro-stimulation of direction selective *MT* neurons had strong effects on the subsequent choices and *RTs*, biasing the monkey toward more, faster choices in the preferred direction of the stimulated neurons and fewer, slower choices in the opposite direction
 - in practice, stimulating a *MT* neuron can be seen as a way to provide more evidence in favour of the direction for which the *MT* neuron is selective, resulting in a biased behaviour of the monkey
 - Conversely, *LIP* micro-stimulation has small effects on choice and modest effects on *RT*, indeed it does not affect the rate of rise of the *DV* but rather pushes it closer to (or further) from the threshold for terminating the decision
 - in practice, stimulating neurons in *LIP* can be seen as a way of accelerating the *RT* for right-choices (and decelerating it for left-choices) by enhancing the drift steep towards the boundary
 - still, this process does not strongly influence the actual final choice because, even though more slowly, the left-choice *LIP* neuron will prevail on the other one for leftward movements



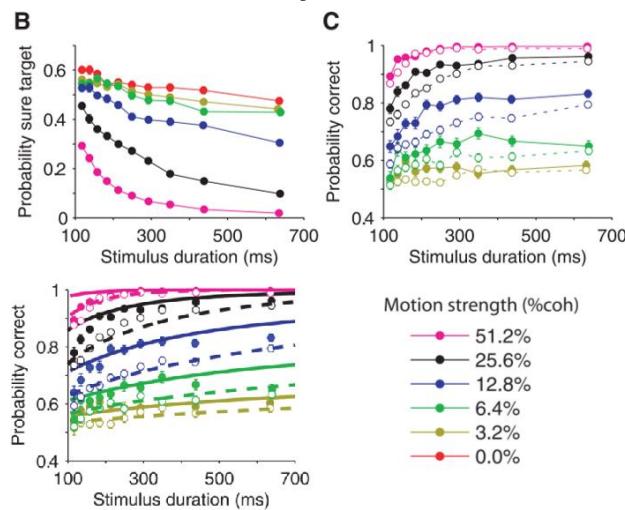
NEURAL CORRELATES OF CONFIDENCE

- Up to now, we have studied the neural correlates of *PDM* trying to find which areas of the brain progressively compute variable that will eventually be used to perform a choice based on the gathered evidences, namely which areas of the brain is in charge of *maximizing the objective accuracy* of identifying the stimulus
 - On the other hand, what remains unclear is where to locate the *subjective confidence* of an individual, and how this plays a role in discrimination tasks
 - with **confidence**, or **choice certainty**, we mean the degree to which a decision-maker believes a choice to be correct or, in other terms, the graded and probabilistic assessment of expected outcome
 - very far from being just an internal matter, **confidence** affects a variety of cognitive functions, from how we plan subsequent actions to how we react and learn from mistakes/successes

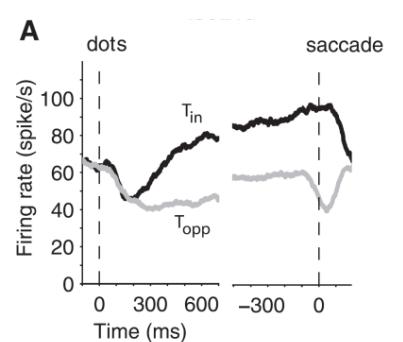
- In order to study that, Kiani *et al.* proposed a variation of the *RDM* paradigm in which, after the stimulus presentation, which varies in duration among the trials, on a random half of them monkeys are given the option to *abort the discrimination task* and to choose, instead, a small but certain reward associated with a third saccade target
 - this “*sure target*” is shown during a delay period, of at least 500ms, after the *RDM* is extinguished, so that the monkey is still forced to come up to a conclusion, as it will not know whether the sure target will be an option or not
 - ideally, the monkey would choose the sure target when its confidence about the discrimination task is low, while when having a higher confidence it most probably decide to take the risk (*bet*) in order to get a greater rewards



- Kiani *et al.*, 2009: the previously explained variation of *RDM* is presented to monkeys while recording a pool of neurons from *LIP*
 - Before looking to the neural correlates, it is important to take a look at the macroscopic responses of the monkeys, from which we can see that
 - the percentage of times in which the monkeys decides not to bet, i.e. to accept the *sure target*, decreases accordingly to the duration of the stimulus and to the motion strength, conversely to the probability of correct guesses (the *accuracy*), which instead increases
 - indeed, as expected, if the stimulus is more coherent and/or it is presented for a higher amount of time, the monkey is more confident and, thus, decides not to accept the small, sure reward but to risk for the bigger one



- interestingly, however, from the last chart we can see how when the monkeys were not given the possibility to choose the *sure target* (dashed lines), namely they were forced to make a choice, their accuracy was slightly but significantly smaller with respect to the trials in which they were given the possibility to choose the *sure target* (solid lines)
 - as this improvement appears at almost all motion strengths and stimulus durations, this implies that the monkeys did not choose the sure target on the basis of stimulus difficulty but, instead, based on a *sense of uncertainty* on each trial
- Proven that the monkeys are behaving in the correct way, namely choosing the *sure target* whenever they do not feel confident enough, we can now have a look at the neural correlates of these choices by studying the neural activities of the pool of *LIP* neurons depending on whether the possibility of choosing the sure target was given or not
 - when the possibility was not given, the neural activity goes according to what we already knew, indeed *LIP* neurons starts to accumulate evidences in favour of the preferred direction (T_{in}) rather than in favour of the null direction (T_{opp}), triggering a saccade only if the evidence in favour of the preferred direction was enough to make the number of spikes per second reaching the barrier



- in contrast, we can see that when the possibility was given, the monkey preferred to choose the *sure target* (T_s , the central curve) whenever the activity of the neurons was neither so high to justify choosing T_{in} nor low enough to justify choosing T_{opp}
 → also, either the monkey chose the T_s option or the T_{opp} option, eventually the activity of the *LIP* neurons would converge to the same level, indeed these neurons are able to trigger a saccade in the preferred direction only, while in the other case the monkey will make a saccade in the direction of the *sure target* (upwards) or in the null direction respectively, something that a different pool of *LIP* neurons take care of
- Finally, even though this is not completely certain, we can say that there are many evidences according to which perceptual choices in the brain follow the so-called *race model*, in which there is not a single *DV* for two hypotheses but rather two (or more) *DVs*, each one supporting one of the possible hypotheses
 - This model is convenient, at first, because it allows the mechanism to extend to decisions among more than two options as a matter of expanding the number of races, and also because it introduces some flexibility into the way the bound height is implemented in the brain
 - Indeed, even though, as for now, we have considered the boundaries to be fixed, there are evidences that support the thesis according to which the brain is able to adaptively reduce the width of the boundaries as time goes by
 - the brain is able to achieve this by adding a **time-dependent** (evidence-independent) **signal** to the accumulated evidence, which we refer to as an "**urgency**" signal
 - the urgency signal does not actually bring the bound closer to the *DVs* but rather **adds to the accumulated evidence in all races** in order to bring each *DVs* closer to the bound, still, the result is the same one, namely that it causes decisions to terminate as time elapses, regardless of the evidence

