Sensory motor integration - Battaglini

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Contents

Chapter 1

Spinal reflexes

Placing together sensation and movement = integration. What is a sense? It is a kind of energy which can be recognized by our body. That part is the part which biulds our senses and we need some devices to recognize and transduct this energy into bological activity (action potential): we have *receptors*. then we need some pathways to communicate the energy to the CNS, so an *afferent pathway*. All thesensory pthways are doen by 3 main neurons: the first is outside the CNS (ganglion of the dorsal root of the spinal cord), the second is maybe in the dorsal horn of the spinal cord or it can also be in the brain stem (gracile and cuneate nucleus). The third neuron is always in the thalamus and from there we go to the cerebral cortex. This is what a sense need.

We know 5 senses, but we also have temperature which have these properties, as well as proprioception (which has receptors in muscles, joints). What about equilibrium? Nothing to do with the other senses, but same modalities; pain is the same. So, the senses are more than 5, at least 9. Most of the time the detection of the enregy can stop at the level of consciousness (good smell, good tase, so not much integration), but may times the sensations give rise to movement. The simplest kind of integration is *reflexes*: we have a low level of integration and then along the spinal cord weìll arrive to the brainstem, to the cerebal cortex where we have conscious movement and we don't need sensory informaion.

1.1 General organization of the spinal cord

In the *lateral horn* (toracic tract) we have the orthosympatethic division of the autonomic nervous system. Revise the cell types in the grey matter and the fibers in the white matter: neurons are placed in the grey matter in different lamina (Rexed's lamina): the motorneurons, in particular α-

motorneurons lamine IX are the most important neurons of the body to communicate with the extenal environment. They make the largest fibers in the spinal cord.

1.1.1 Classification of peripheral fibers

We need to know names!

The diameter of fibers in spinal nerves is different: form less that 1 micron to more than 20 microns. There is a strict relatioshp between the diameter and velocity of conduction of the nerve fibers:

$$v = 6d\,, \tag{1.1}$$

where v is the velocity in ms and d is the diameter in μs. The largest fibers are those on α-motorneurons. We have 2 classifications, the first based on the velocity of conduction[1]:

- A, subdivided into
  - A-alfa
  - A-beta: sensory fibers which carry information for touch, pressure, vibration. They are smaller (6-12 micron)
  - A-gamma: originates from the γ-motorneurons. These motorneurons are involved in the monosynaptic reflex, they innervate the spindle
  - A-delta: they deal with pain, a quite complicated sense because it has an emotional component which no other sensory modality has. The real name is *nociception*, perception of noxious (nocivo) stimuli. Pain is an emotional component which is added to nociception
- B: preganglionic fibers (autonomic nervous system)
- C: the smalles fibers at all, they carry pain informations

BY this classification we can get ifthe receptor can be modulated or not, if it can have one or more variable. Chemica synapses are the bases for integration. The other classification is done by anatomist based on the diameter of the fiber:

[1]Take nerve fiber, apply stimulus and record composite potential far from the stimulating point.

- IA, IB
- II
- III
- IV

We will use mainly the first one, the second only for the fibers of first type because this population of fibers carry different information, so in order to recognize fibers which carry different information we use different names. Speaking of large fibers with high velocity of conduction which originates from α-motorneurons, we talk about A-alfa fibers, but we have also sensory fibers that can originate from spindle and gogli tendon organ, and we call them IA and IB respectively. So, IA means iber with large diameter, high velocity conduction, which came from spindle.

Pain comes from 2 different pathways, A-delta fibers and C fibers.

1.2 Monosynaptic reflex

Reflxes are a nice way to regulate something. Everytime we want to maintaint the variable at a fixed level, we need a reflex. We need a detector of the stimulus, something to regulate the variable and an integration system. We need 5 actors: receptor, afferent pathway, integrative center, efferent pathway and effector.

The most important thing is the *integrative center*, which gives the power to choice what we want. It will take into account for example the temperature of the room, our will and the time, but we can add features, for example a student counter. We can adapt the system based on our needs, so we can classify the system in order of how many synapses with the interation center it has: monosynaptic reflexes, disynaptic reflexes, polysinaptic reflexes. The number of synapses changes according to the strenght of the stimulus. We can have *esteroceptive reflexes*, reflexes that have the energy outside the body (vision, touch); we can have *proprioceptive reflexes*, where the energy is inside the body; then energy still inside the body in viscera, gut, splancinc system which are *enteroceptive reflexes*, for mainstaing blood plessure, the content of oxigen in the blood etc. This is the funcitonal classification.

We need some tkind of energy, a receptor which can deal with that kind of energy, the afferent pathway, an integration center which is always in CNS and then the efferent pathway and the effector: this is the reflex.

1.2.1 Muscle proprioceptors

The spindle gives origin to the simples reflex, the *monosynaptic reflex*.

Inside the muscle we have the spindle, which is the actual reflex: it is a small number (8-10) of muscle fibers that are enveloped inside a capsule of connective tissue. These fibers differ from extrafusal fibers because the striature aer only at the extremities, not thta much in the centrum so the extremities can shorten when excitted but not the central region, so when muscle contract the total lenght does not change, but the polar region do, shorten at the epenses of the central region. These fibers are not all the same, some are enlarged in the center, some don't. It is a receptor, so it needs to have sensory fibers (and motor fibers) which enters the capsule and go all around the central region of the receptor itself. There are different kind of muscle fibers inside the spindle: *bag fibers* and *chain fibers*.

In chain fibers the nuclei are placed one close to the other almost along all the fiber,[2] while in the bag they are in the center of the fiber. Bag and chain are sensory fibers: we have IA fibers of the spindle, diameter from 12 to 20 microns and carry AP up to 120 m/s, and II fibers which are a bit far fro mthe central region. The sensory fibers enter the spindle and ges around like a ring in the center of the spindle. That is the primary receptor of the spindle, a mechanic receptor which responds to mechanic stimuli, to stretch. Its sensitivity can be modulated by the NS,

Let's see a little piece of the IA fiber: the membranes has channels that are not specific channels, when they open both Na and K can cross them. If these channels open, we have depolarization, but they are normally closed, but they are linked each other by proteins, they are not free to float in the membrane like the other channels. When we apply mechanical stimulus to the membrane, we change the shape of the membrane and the channels are stretched by the fibrous protein which link them one to the other, so they open! This is a *mechanical transduction*. The proper stimulus to activate the receptor is to *stretch the spindle* in order to open these channels: the sensitivity to stretch is increased by the rings of sensory fibers that we have along the muscle fibers. As many ring you have, as much sensitivity we have, because it is an amplification.

When is the spindle stretched? The spindle is inserted in parallel with the muscle fiber, so we need to stretch the entire muscle to stretch the spindle. The nervous receptor is the part with the rings, but in order to stretch the rings we need to stretch the spindle and to stretch the spindle we need t stretch the muscle.

There are also secondary sensory fibers which do the same rings but not in

[2]Muscle fibers are polinucleated fibers.

the central region of the spindle, they are II or B fibers. The difference with IA is that a popuation of IA is senstive to dunamic stretch and II fibers are preferentially sensitive to continuous stretches. The spindle discharge also when the muscle is relaxed, why? Because also when the muscle is relaxed, the muscle is in any case a little bit stretched: think about when we go to the mountain for skiing and someone broke the bones of the leg, the bone is not in its normal position and it has o be stretched again to be placed in the right position. This is known as *static discharge*, all the time that the muscle is stretched we have a discharge, but it also discharge when we apply a *dynamical* stretch, in which the response is limited to the time of stretching. Which if the 2 discharge will be responsible for the stretch reflex? The dynamic.

In the graphs we see the discharge of the spindle when a stretch is applyed to the muscle: we maintain the muscle in the new position $\longrightarrow$dynamic discharge and when the muscle is in the new position we have a nwe steady-state of the muscle. The dynamic response is mainly due to IA fibers which makes the ring in the beg fibers, while the static response mainly to the chain fibers. Globally, the spindle responds both to dynamic and static stretch. The response is due to the sensory fiber that rings to the spindle fiber[3].

What happens when I shorten the muscle, for example contracting the byceps? Fibes become shorter and the spindle does no longer discharge. THe spindle dscharge if I increase the lenght of the muscle, but does not do it if I shorten the muscle! How can I change the sensitivity of the spindle is such a way that it can respond for every lenght of the muscle? I can make the spindle fibers shorter, it wil lcontinue to respond. I adjust the lenght of the spindle with the lenght of the muscle. In this way, I have to apply a stimuli to the muscle fibers inside the spindle, which are γ-motorneurons, not to the entire muscle, then I placed the central region under tension, it is stretched, and once it is stretched it will come back to discharge. Thanks to γ-motorneurons, which are not linked to the periphery but from the lateral vestibular nucleus, the spindle is always active, but how can I distinguish the second situation from the third situation? Maybe there is a difference in structures that govern this system: it is me that decide to shorten the muscle and when, to activate the γ system. I know whether there is or not a gamma activity, because it's me that produce γ activity whenever I produce α activity. This is conscious! If I receive IA activity during γ activity, I understand that the muscle is shortening, but if I recieve IA actiity wuthout gamma activity, it means tha the muscle is stretching! It's me that gives origin to α and γ activity.

put the figure on the phone

[3]kandel pag 795

This is to maintain the sensitivity of the spindle independently from the lenght of the muscle. We brain discriminates the firing due to shortening of the muscle to the firing due to the contraction. I have a resting information and also I need to be aware when muscle changes its length: that's why we have different fibers for dynamic or static changes but also different γ-motorneurons for static and dynamic.

What happens when I increase the discharge of the γ-motorneuron? If I activate the static one, I activate the mtorneuron before the chaning in leght, the spindle does not change it lenght, simply the muscle region inside the spindle contract (distal region) and stretches the central region $\longrightarrow$increase in discharge. Then I stretch the entire muscle and i have a repsonse that stabilize at a higher level, but I have the overall changes is small. We also have systems in which the overal change is higher, this is the dynamic one. Both of them are present in the spindle, but the system which better signals rapid changes is the one that gives origin to the monosynaptic reflex. The static system is less important, it is important only to maintain the postural tone, a degree of contraction always present in any muscle, which is higher in muscles which have to fight against gravity. These muscles are named *antigravital muscles* and work more than the other muscles.

At rest, the muscle has its length (stretched) and we have some degree of discharge alonf the sensory fiber. This fiber makes synapse with a motorneurons which maintains the contraction of the muscle. This changes if we rapidly stretch the muscle (monosynaptic reflex or myotatic reflex): every muscle show this kind of reflex, but it is earier to evoke this reflex in the quadriceps because it is very large and has many spindles. We stretch the spindle inside the muscle using the anatomy: the tendon includes the msucle and the rotula and we can use an hummer below the rotula because there is a cavity inside the capsula and when we press the tendon inside this cavity, the tendon is not elastic and so I stretch the muscle. The other possibility is to hit from the high of the rotula, but the result is the same. In response, we extend the leg. Afferent fiber, α-mootneuron, contraction of the muscle and extension of the leg. We have in the spinal cord more synapsis, because the activation f the α-motorneuron affects the attivity of the antagonist muscle $\longrightarrow$the same fibers that enters the spinal cord and goes to the reflex also inhibits the antagonist muscle via an interneuron. The same things happens with the antagonist muscle (in this case the Hamstring, a flexor). This is a *reciprocal inhibition*: each α-motorneuron inhibits the antagonist one. This is not a monosynaptic reflex, because I have a di-synaptic inhibition, but the definition of reflex is the response of a muscle to a proper stimulation. When we say contraction or activation of a muscle in response to a proper stimulus, in the stretch reflex the response in the movement of the leg, not

the inhibition of the antagonis! The reflex is the shorter pathway and, in this case, a monosynaptic reflex.

A spinal reflex is the response of a muscle to an appropriate stimulation that depends on specific receptors.

Why do we need this kind of reflex? It is the strongest reflex we have, the fastest afferent pathway, the fastest integration, the fastest efferent pathway, so the fastes reflex we have. Why is it so fast? When we add weight to the tray, for a moment we ave a stretching of the muscle but immediately the spindle adapts and returns to the previous position. This is a regulatory system to maintain the position of muscle! That's why this is so important. For example, when we walk/run we don't fall down because we replace quickly the leg into its position, so maybe the reflex develop to maintain the walking and running, so it must be very very fast. Then we have the other problem that when you shorten the muscle, the frequency of discharge reduces and eventually stops, but we don't want that because in this way we loose information about the lenght of the muscle. The solution is to shorten the muscle fibers inside the spindle when the muscle is shorten, so the central part wil lbe stretched and we have a γ control and we increase the frequency of discharge. The spindle is the oly receptor in which we can change the *sensitivity*.

It is CNS that decides to activate α-motorneuron and to increase activity of γ-motorneurons. Alpha are connected to the periphery, gamma does not, they receive information from inside the brain. Gamma motorneuron receive infomraiton from the lateral vestibular nuclei in the brainstem, which receives information form the cerebellum. So, cerebellum $\longrightarrow$lateral vestibular nucleus[4] $\longrightarrow$spinal cord (γ-motorneurons). It is the cerebellum which determines the activity of these motorneurons. A descending pathway to control the α-motorneuron is the lateral cortical path (pyramidal system) and the extrapyramidal system.: these 2 systems allow the cortex to drive motorneuron. The vestibular-spinal tract (from lateral vestibular nucleus to the γ-motorneurons) is part of the extrapyramidal system: when I wish to make some precise movements with the hand, I use the pyramidal system which goes fast to the motorneurons of the hands, and I don't want to care about all the other muscles that are involved $\longrightarrow$this is done by the extrapyramidal system. The spindle will contract and the discharge will increase $\longrightarrow$increase of the tone of the muscle to support what we want to do with the hand. The tonic discharge of α-motorneurons depends on a discending path and also on the Ia afference, which is driven by the spindle which is driven by the activity of the γ-motorneuron.

[4] A cerebellar nuclei outside the cerebellum.

(7.04.2015)

Monosynaptic reflex means that the presynaptic neuron makes only one synapse with the post-synaptic motorneuron, not that in the reflex there is only one synapse. Every muscle can show this reflex! The receptor is the muscle spindle, the afferent path is the 1A fiber, the integrator is the synapse btw afferent and efferent path, the efferent is the α-motorneuron, the effector is the same muscle where the spindle was.

We have less γ-motorneurons than α-ones, they are smaller and also their fibers are smaller, so I can drive γ-motorneouron involving less fibers than those needed for α. They are less expensive, but not less effective: when we arrive at the muscle, there is an *amplification*. Ia afferences go to all the α-motorneurons of the muscle, while I need few afferences to the γ-motorneuron to amplificate its signal in the muscle. There is a problem in this amplification: if I want to have a precise and delicate, graduated contraction of the muscle, I cannot use the spindle system because all the alpha-motorneurons are involved with this amplification. With the gamma system I can only have muscle movement, not percise movement, contraction that involve all the muscle. γ motorneurons and spindle are so few that in no case the gamma activity can make the muscle shorten. The only effect of gamma-motorneuron activation can be a *change in tone*, not a movement, because they are few in spinal cord but they involve the few spindles which involve all the α-motorneurons (so they are not good for fine movements). The pyramidal system change the position, the γ-system maintains it. This is synaptic integration and the amplification is done by the few spindles which innervates all the alpha-motorneurons. The integration is what happens on the membrane of the α-motorneurons, while the γ-one is the amplification. For example, 10 gamma-motorneuron that innervates 50 spindle (every gamma goes to more than one spindle), then to 10000 alpha-motorneuron: this is the amplification.

How can the γ-motorneuron have a sensory function? How can I know the lenght of a muscle without involving gamma? Via the antagonist muscle, but we still need informations from the spindle, so we need to maintaint stretched the central region of the spindle (this is achieved via gamma-motorneurons). This is the sensory function of gamma-motorneurons, to maintain sensitivity.

Gamma-motorneuros have an important function in maintaining the steady-contraction of a muscle. If I cut the dorsal root of a cat, the cat cannot have experience of the touching of its body. The cat can move, but it has no knowledge of its position in the space. The tone cannot be maintained because gamma-motorneurons are intact, but they cannot speak to the alpha-motorneuron since Ia fibers have been cut.

Why do the physician evoke this reflex? To have an idea of the integrity

of spinal cord and CNS, but it is important the *central excitatory state*, which is different from one person to another and inside the same person at different moments. Alpha-motorneurons are the final common pathway, so if we have a high central excitatory state, so a shor reacttion time along a polisynaptic pathway, alpha-motorneurons will be very reactive. If we have a low excitatory central state, few AP reach the alpha-motorneuron and the response will be poor. In a neurological visit, the neurologist will search for many monosynaptic reflexes to explore as many part as possible of the spinal cord and see the degree of reaction. We can voluntary change our response to the stimulation of the periphery!

1.2.2 H reflex

H stays for "Hoffmann" reflex. A person with ataxia, with difficulty in producing movement, could have a compression of a nerve. We can evoke this reflex, a clinical way to produce the monosynaptic reflex. A spinal reflex cannot be modulated if we cut the spinal cord: we have a complete atonia, loss of muscle tone and loss of reflexed, because we are removing some descending pathways. After a while, the reflexes will wokr again and will take the place of the pathways that have been cut.

To study it, we make an *electromiogram* EMG, the registration of the electrical activity of the muscle, then apply stimuli to the nerve and record the response from the muscle. We have one response at low intensity, the *M wave* where M stays from muscle: we have directly excited the α-motorneurons. Then increase the inesity of stimulation $\longrightarrow$a second wave, the *H-reflex*: the pathway that evokes it is driven by the primary sensory afference of the spindle which has been activated electrically , we activate the 1a fiber. The delay btw these 2 waves depends on the interity of afferent and efferent pathways and spinal cord integrity. If we are not able to activate the H response, there is something wrong in the spinal cord (because the afferent and efferent are in the same nerve and we are applying). If we are unable to evoke also the M response, we have a problem in the nerve. If we make a lesion in a section of spinal cord and we look at reflexes up and down the lesion, we have reflexes! In a paralytic person, reflexes still work, but the person cannot make them work voluntary. Of course, a degenerative pathology of the motorneuron will give a negative outcome of the test.

1.2.3 Reciprocal inhibition

All the time we activate one muscle, through interneurons we inhibit the antagonist one

1.3 Di-synaptic reflexes

Sherrington discovered this reflex. If you make sections of spinal cord or brainstem, you have different effects on the periphery. Section of spinal cord $\longrightarrow$flaccida paralysis. Section of brain stem $\longrightarrow$spastic, rigid paralysis. If a section in between the superior colliculi, a very easy point to make sections because you follow the tectorial membrane and arrive there. When doing this, the animal undergoes spastic paralysis. A primate or human would have a different behavior: the cat/dog will extend the 4 paws, while in primates we have extension of the leg but flexion of the arms (to be antigravitatory). Forcing the leg to flex, initially it was a problem but after a while the leg could be moved but then came back to its position. Why? Because in the muscle we have a second proprioceptor, the *golgi tendon organ*, placed btw the muscle and the tedon. It is a first type receptors with free nerve ending. We have afferent fibers which enters and goes insithe the collagen of the tendon. It is a proprioceptor, a stretch receptor because, to be activated, its nerve endings has to be stretched. It is places *in series* with the muscle, so everytime the muscle contracts, the golgi tendon organ is excited.

The 5 elements in the reflex are: recpetor (golgi tendon organ), afferent fiber (1b fiber, the same as 1a but have a different name to distinguish them from the 1a i nthe spindle),[5], theu the first synapse btw 1b band inteneruon, a second synapse btw interneuron ad α-motorneuron of the same muscle where the receptor is. To activate the receptor, I can extend the arm (the tendon will stretch the receptor) or contract the muscle (I have to stretch the tendon, the first is from the bone, the second from the muscle).

Since there is a synapse btw afferent and motorneuron ,the response to stretch of the muscle will be an inhibition of the motorneuron because there is an interneuron. Everytime I stretch the muscle, I have an inhibition of it. Its role is not clear: maybe it prevents a damage of the muscle when stretch is too much.

Sherrington, sectioning the brain stem btw inferior and superior colliculi, it separated 2 different regions of the reticular formation. Cell bodies are more far one from the other in reticular formation, even if it occupies the entire brainstem. The more caudal part of the reticular formation has an excitatory action on the α-motorneurons of antigravitatory muscle, so the part below the section excites these motorneurons. The part that was sectioned, was inhibitory, so the animal went in spastic paralysis. When there is no section, there is equilibrium btw excitation and inhibition and we maintain

[5] 1a, A-aplha and 1b are the same thing but for spindle, motorneurons and tendon organ.

the tone. Then sharringot went to move the arm: the antagonisthas the golgi tendon organ activated, but maybe not so much, then sharrington tryed to flex the arm and this activated the golgi-tendon organ $\longrightarrow$inhibition of α-motorneuron, so contraction of the muscle stops and it is easy to continue the action, there is no opposition of the muscle. Then the muscle is relaxed, so the golgi tendon organ is less stretched than before $\longrightarrow$the stimulation goes back under threshold and does no longer discharge, so α-motorneuron is not inhibited and the circuit does not work$\longrightarrow$excitation from reticular formation is again effective $\longrightarrow$spastic position.

In the reticular formation there are 2 art: a rostral, inhibitory on muscle tone, and a caudal, excitatory. It is a reflex that helps the muscle not to be overstretched and not to break it, but its role is still controversial.

1.4 Polisynaptic reflexes

(12.04.2016)

The best known is the *nociceptive* reflex. The majority are flexor reflexes and are evoked by nociceptive stimuli: it is a stimulus which evokes damage to a part of our body (in this case, the skin). The response to a nociceptive stimuli under the foot is the flexion of the leg: we need to recruit more than one muscle (first difference from mono and di-synaptic reflex, where I recruit the muscle that it innervates but also I inhibit the antagonist, but the definition of the reflex is that the reflex is the response to a proper stimulus, and the response is an active response, not an inhibition, so these 2 reflexes involve just one muscle). We not only have to rise the leg, but the other leg has to account for the double of the weight of before!

I have the stimulation of the receptor, which are free nerve endings; the afferent fibers are very small fibers (Aδ), which have the cell body in the dorsal root ganglion; the integrative center is the spinal cord itself, because this reflex involves many muscle and that's the reason for which these reflexes are considered *polisynaptic* and the number of the synapses changes with respect to the strenght of the stimulus; the efferent pathway are motorneurons; the effectors are the muscles innervated by the part of the spinal cord from which the motorneurons start.

We apply the stimulus, discharge goes along afferent pathway to the spinal cord, the information enters in the dorsal horn and we have the contraction of flexor muscles, because flexors takes away the part of the body that isleisoned fro mthe stimulus (it takes it near to the body); we have reciprocal inhibition and we have inhibition of the antagonist. Informaiton has also to go in the opposite side, in order to make the other leg more resistant to gravity, so

we have inhibition of the flexor muscle of the opposite site and contraction of the estensor. If the stimulus is stronger, we make a larger movememnt, so we can recruit more and more muscles following a more intense stimulus. That's why I cannot count the number of synapses, because it depends on the intensity of the stimulus.

Let's imagine the information that enters in the spinal cord immediately stops and the rest of the circuit is governed by interneurons: if this interneuron is driven by descending pathway instead of by the periphery, which will be the response if the activation come from inside (cerebral cortex) instead of outside? It will be the same movements, because the neurons which are involved are the same! On the opposite side there will be the same circuit. If I activate the same kind of interneurons on the opposite side, I walk! Many people thinks that the integrative center of the polisynaptic reflex is what we use for walking, a rhythmic movement. Maybe the voluntary component resides in the frequency of the wsteps and with the stop of the activity. The integrative center of the polisynaptic reflex may be used to fight gravity but in a dynamic way.

Let's think of an animal that walks with 4 legs, like a cat: it has a noxious stimulus to one leg, so it lift the leg and the response is to increase the tone in the opposite leg, but the animal can fall on the back: to avoid it I will increase the tone of the opposite leg in the other side. Stimulus in the anterior dx paw, so the response is the inrease of the tone in the anterior s paw; I'll have the same in the posterior dx paw, in this way the animal can stand. If the stimulus is strong enough, it can involve all the spinal cord. It happens also in human (deambulazione) that hte integrative center extends to all the spinal cord.

So, the integrative centers can be small of big with respect to the frequency of the stimulus.

1.5 Synaptic organization of the spinal cord

Coding of the intesity of the stimuli: recruitment of muscles according to the intesity of the stimulus. How does it happen? It is called *population effect*: if the intesity of the stimuli is not that much, we'll recruit some of the fibers in the skin (free nerve endings) and possibly just few neurons in the spinal cord, those which have a grater denesity just below the stimulus. If we increase the intesity of the stimulus, we'll recruit more skin and more fibers and more neurons will discharge.

A single neuron can discharge at a given frequency: the highest theoretical frequency is 1 kHz (1 thousand AP per second). If the intesity is high, the

recruitment of neurons is higher. How can the NS code higher frequency than the single neurons? Because of population effect. How can the cerebral cortex understand that the stimulus is strong or not? And compared to another weaker stimulus? On the strong stimuli, we have a gradient of activation: the neurons in the center of the spot will discharge at the higer possible frequency, those far away will discharge less. If we have a large stimulus, we don't have this. Possibly, experiment simulating this gradient: maybe our system can code a *gradient of excitation* as a sharp stimuli which works at high intensity. So, population helps to code the intesity. It is a matter of learning: when we have that kind of activation on the cerebral cortex, it is a sharp stimulus.

Inside this phenomenon we also have *spatial sumamtion*: if we activate the afferent fiber, the neuron will discharge if it has a lot of synapses, it may discharge or not if the synapses are less.

Let's imagine to need the activation of 3 synapses from neuron 1 to activate neurons A and 4 spikes: if we have 2 spikes on the presynaptic fiber, it will work becuase we'll have 2 AP per synapses, so 2×3: this is *temporal summation*. If I have a neuron B which have 2 synapses, one from neuron 1 and one from neruon 2: if I have no spikes on neuron 2 and 2 on neuron 1, I'll have no AP in neuron B. If neuron 1 and 2 produces 2 spikes respectively, I'll have a spike in B: this is a *spatial summation*, becuase the spikes come from different neurons. The neurons which discharge are those in the discharge zone of the afferent fiber (neuron A), whicle neuron B is in the *subliminar area* of discharge of neuron 1, so it needs something more to discharge. .

put figure sul quaderno pattinaggio

All the time we enter a nucleus, like gracile and cuneate nuclei in the brainstem, we have the same: some degree of convergence and some degreee of divergence.

1.6 General organization of the motor system

The afferent fibers does not finishes their job in the reflex, but goes up to other part of the NS, like brain stem. This pathway enter the skull and reaches brainstem, thalamus, cerebellum. In brainstem it goes in the reticular formation, that sends these informations to the diencephalon and then to the cerebral cortex. to reach special areas for proprioception it is important to reach the thalamus to go to the somatosensorial region, which is in the parietal region. We have fibers going to cerebellum, that is not invlved in perception but it is involved in movement.

Brainstem sends back infos to the spinal cord and we also have the lateral vestibular nuclei, very important for postural tone and control of muscle

with respect to gravity, it is related to γ-motorneurons having a facilitatory effect. The main information to the lateral vestibular nucleus is from the cerebellum. there are no neurons that goes directly from the cerebellum to the spinal cord because the main output of the cerebellum goes to thalamus (ventral lateral nucleus). This system of fiber from cerebellum to thalamus from the superior (the medial one has only afferences to the cerebellum). The thalamus does not sends back information to the spinal cord: it is the only input to the cerebral cortex, which sends informations to cerebellum, brainstem, motorneurons in spinal cord.

Chapter 2

Brainstem

Dorsal view of brainstem. Reticular formation is present also in the spinal cord (grey matter is enveloped in a small layer of reticualr formation).

2.1 Vestibular reflexes

Devoted to adjust for the equilibrium. For ear, we have the external ear, middle ear and internal ear.The acustic function is played by *cocles*: sounds are collected through the external ear, goes trought the timpanuc which vibrates: vibration is collectes by martello, incudine e staffa and it is transmitted to coclea, which is filled with fluid that moves and make a membrane in the middle of the coclea (basal membrane) vibrate: cilia vibrates and this mechanical transduction brings acustic information.

revise anatomy

In the same location of coclea there are other structures, the *semicircular channels* which are 3 and are responsible for equilibrium. They also are filled with endolinfa, they are receptors and are placed on different planes of space to cover all possible deflexion in 3D space. They are structured inside the bone, they originate by an enlargment in the bone itselfe, where there are 2 small regions, *utricle* and *saccule*, where there are receptors as well as on the basis of semicircular channels. Every channel has 2 branches with which it comunicates with the larger region: one of the 2 branches has an enlargment where there are receptors. So, we have 5 groups of receptors in vestibular system: saccule, utricule and one in each of the semicircular channels.

Let's look at a semicircular channels: we have the bone all around, a membrane and linfa inside. The receptors are neurons which have cilia, second-type receptor: cilia are the transductive portion of the receptor, because they can be moved in one direction or the other and moving, they open ion channels on the membrane itself. One of these cilica is longer that

the others: if cilia move toward the kinocilium (longest one) we have depolarization and open channels, if they move in the other direction we have hyperpolarization. Cilia are enveloped inside a structure called *cupula*, a solid gel structure which covers completely the cilia and occupies all the region of the channel, closing them. All around we have linfa.

How do they work? If I rotate the head, I move the bone but the linfa will not because water does not easly move if the container moves: when this happens, the cupula is pushed by the linfa that do not move, so the receptors discharge and they can detect any kind of movement of our head. These are *dynamic receptors* because they only discharge when the head moves, becuae when the head stops the cupula comes back to the normal position.

These receptors are not responsible for the proprioception of the position of the head in the space, for this we have saccule and utricule: they are stereocilia which have to be moved in one direction or the other, we have a flat gel that covers the cilia and over it we have *otoconia*, small stones which are placed on the memrbane of the gel itself. When we move the head, stones follows the gravity and move accordingly and stimulate the cilia; when we change position, stones move the cilia in another position. Cilia are static receptors, they give informaiton of the position of the head time by time.

We have superior, medial, lateral and inferion vestibular nucleus: all of them receives informations from the receptors. LVN is mainly involved in the vestibulo-spinal tract which is cotrolling tone against gravity: we need to change the muscle tone against gravity for the equilibrium. Informaiton from the VN goes to the nuclei of the external eye muscles, abducens, throuchlear and oculomotrn nuclei. Changes in the position of the head bring to changes of eye movement, so I can maintain fixation of something of interest in space independentl of the movement of the head. Vestibular reflexes are involved in maintaining the fixation during movement.

2.1.1 Vestibular nystagmus

It starts from the vestibular apparatus. Orizonal movement, slow eye movement in one direction followed by a rapid coming back to the initial position. It is what we experienced when we rotate longtime on ourselves and we feel confused. We stop the head, the linfa continues to move and also the eye, but we are aware of standing, we know we are not moving, so the brain receives strange informations: images are moving and I'm standing.

Vestibular nystagmus is important also by the clinical point of view: the reflex involves huge portion of the brainstem, almost all the brainstem. All the time a neurologist think that there might be a problem in the brainstem, it tries to evoke vestibular nystagmus: if it works, meybe the brainstem

is safe. How to evoke it? Make the patient's head confortable ad drop some cold water in the ear and this make convective movements in the linfa $\longrightarrow$vestibular apparatus is stimulated and the patient shows nystagmus.

2.1.2 Optocinetic nystagmus

It originates from the eye, it is an optic nystagmus. It happens when we are in the railway station, sitting in the train and the train moves, but we realiza that is the other train that moves: a region of the retina is stimulated by movement and our system percieves that images are moving on the retina and the only interpretetion possible is that we are moving. How does it happen?

Because some fibers from the retina do not take the principal pathway (lateral geniculate nucleus $\longrightarrow$cerebral cortex) but goes to the *vestibular nuclei*: there are very few fibers, so we need a great part of the retina excited. From the vestibular nuclei we start the same pathway for the vestibular apparatus $\longrightarrow$eye movememnt $\longrightarrow$interpretation is movement, but it is a mistake of the brain because the brain works on what is more frequent in its experience. The stronger one is the vestibular nystagmus. Not all the vestibular nuclei are involved in the vestibular reflexes: the lateral vestibular nucleus sent afferent fibers to the γ-motorneurons, to maintain the posture. Posture has to do with equilibrium and informations on equilibrium comes from the vestibular nucleus; it receives the informaiton form the cerebellum.

2.1.3 Vestibular cortex

From brainstem nuclei to thalamus and vestibular cortex at the bottom of the lateral fissure of Silvio, so a part in the parietal cortex and a part in the temporal region.

2.2 Orienting reflex

(19.04.2016)

It regards the eye movements and it brings the eyes towards something which appears or moves in the visual environment. Orienting the eyes toward something that is entering our visual field. We need this reflex: inside the eyes, we have a very small region of goog quality of vision, the *fovea*. How large it the fovea? It is $1\,cm^2$ at 1 m of distance from the eye. Why such a small fovea? From the outer part of the eye to the inner part we have the sclera, the white part of the eye, then coroide, the vascular part, the most

irrorated part of our body in terms of flow. Why to have so high flow of blood in the eye? These are veins, so no exchange of materials with the cells: the lens of the eye has a great power to "fire" something and inside the eye the temperature will increase a lot! This great flow is supposed to be used to cool the eye, like a radiator, so a strong system to reduce the temperature. Then there is a layer of epithelium of black cells, the *pigmented epithelium* with a lot of melatonine, to avoid that a race of light reaches the eye and is reflected to other direction, becuase the epithelium is on the back of the cells. Finally, we hve rod and cones: they are excited for the light and transmit informaiton to bipolar cells $\longrightarrow$ganglion cells $\longrightarrow$AP.

AP for gangliar cells go to the surface of the retina, where there are the axons of the ganglion cells which converge at the level of the optic chiasm: the light has to go across all these layers of cells, so the light is deteriorated when it reaches the receptor. There is a region that is different, the fovea: all the cells are splitted laterally, so that the light can directly reach the fotoreceptors. In the fovea, the light reach directly the fotoreceptor and there is the highest density of fotoreceptors. It is the region of *best acuity* in the eye.

We are not aware that we see very well in the fovea and the rest is not so good, because we do not see time by time what arrives on the retina, but we see a representation of the visual environment, done by our brain. It is like a mosaic. We want to maintain updated this representation: if something changes, I have to change the representation, How can I know that something changes? It woukd be perfect if I had a system which detects changes: it brings the fovea in the region of space where the change happened. The visual stimuli is something that *moves*. How does it work?

We have different kind of cells in the retina: the retina comes from the telencephalic region during development, it goes outside the brain before the bone segregates the brain itself. So, these cells are modifyed neurons. Ganglion cells are classified according to the properties of discharge with the alphabetic letters: X, Y and W . X ganglion cells have small bodies, small dendrites. They respond with brisk discharges of AP to small flashes of light that impinge with the receptive field. *The receptive field is a region of space which, when properly stimulated, changes the activity of a neuron.* This concept is not linked to receptor and peripheral neuron. X cells have a very small receptive field, so these cells are mainly involved in the detection of shape of objects in space, because they can have high density and they can recognize the details of an object. The fiber which originates from these X cells and go to the *lateral genicualte body*, an ectopic nucleus of the thalamus. It is the second station of this pathway and it is done by 6 layers of neurons: X cells project to the 3^{rd}, 4^{th}, 5^{th} and 6^{th} external layer. From this they

project to the visual cortex V1 in the medial part of the occipital lobe, in the *calcarine fissure*. Fibers from the thalamus reaches the 4^{th} layer of V1 cerebral cortex: it is a large area, plenty of granule cells, and this is the reason why it is called calcarine fissure, because it is full of these cells. It is named also striate area because the fibers are so many that constitute a layer of white matter inside the 4^{th} area, and we can see this area without microscope, and it is present only in primates.

The Y cells are responsible to spot or line of light which move across the receptive field: they are quite large and not sensitive to shape, so mainly repsonsible for the *detection of movememnt of objects* in the visual space. Their axons, when leaving the retina, goes to the 1^{st} and 2^{nd} layers of lateral geniculat nucleus, magnocellular layers: the other layers are known as parvocellular layers. This system consitue the *retino-geniculate-cortical* pathway, the main one for visual perception. Visual information does not only partecipate to this pathway, bt we have other systems.

Another system originates from W ganglion cells (10% of genglion cells): they have small cell body and larger dendrites than Y cells, they are responsive to spot of light but they are sensitive to larger spot of light, so presence of visual stimulus. These fibers do not project to the lateral geniculate body, but to the *superior colliculus*. These are neurons interlivered by white matter, to build up several laers of grey matter. We don't know how many layers in the superior colliculus: it is very difficult to find the borders of the layers. By the functional point of view there are 4 layers: the most sueprficial one receives informations from the retina and there is also some degree of topography. Then we have a layer which is responsive to acustic stimuli: there is a topography of space. Then a layer for somatosensory neurons, snsitive to touch, and still we have topography. Then the 4^{th} layer which do not respond at all to any stimuli, so it is a *motor layer* for eye movements (if I apply an electrical stimuli). It will move the eye in the direction of the stimuli detected by the other 3 layers, so these layers are in perfect register.

If a visual stimulus appear in space, the W cells will be driven, so the fist layer will be activated, information will go to the 4th layer and the eye will go in that direction: this is the *orienting reflex*. It is the reflex which we use when something drops on the floor and we can easly find it when it moves, but when the objects stops on the ground we need to carfelly look to recognize the object that fell. If it still moves, the eyes will go there even if we don't know what the object is. The brain of the frog finishes at the level of brainstem, they do not have cerebral cortex. This reflex mainly involve the W cells.

2.2.1 Muscles of the eye

For each eye we have 6 muscles, innervated by the vestibular nucleus. 4 of them are placed up-down-left-right and can move the eye in every direction, then 2 oblique muscles responsible for a degree of rotation of the eye in one direction or the other, and they allow a great freedom of eye movement.

If I have to move the eyes, that originates another problem: if I move the eyes, I interfere with the precision of images on the retina like if I were taking pictures. It is a serious problem for the brain. How can the brain guess the amount of deterioration? When we move spontaneously the eyes, perception is stable, but if we do the same movement with the hand I see everything jumping. Why? The sstem has to adjust for perception and movement. What happens is that during the eye movement, this fast eye movement are known as *saccadic eye movement*: vision is suppressed, the cerebral cortex does not receive visual information. Saccads do last 30-40 ms, a lot of time, and we are sure that in the situation of artificial stimuli I see everything jumping, so how is it possible that vision is suppressed? The eye movement is done by our brain, but not the superior colliculus, which is only responsible of reflexe, but from the *frontal eye fields*, region of the motor cortex specific for eye movement, in front of area 4, which is in front of the central sulcus, in the prefrontal girus. The region of the eyes movement is the area 8: it is the area which decides to make a saccad. But why ths information goes to the eye nuclei? Collateral fibers from frontal eye field go to the primary visual cortex and they inform the primary visual cortex that a saccadic eye movement is going to be performed: this is a *efferent copy* of the real message, or corollary discharge, related to the real eye movement. This copy tells the cortex what kind of movement it is, its duration, velocity etc, so the cortex knows exactly how long the movement will lasts.

Primary visual cortex will send info to the lateral geniculate nucleus: these fibers are more than those that goes form the lateral geniculate nucleus to the cortex. These cortical-geniculat fibers inhibit the LGN during saccadic movement. I do not see blank because I see the last image which I saw before turning of the cortex. When the visual cortex knows that the movement is finished, because it receives an efferent copy of the movement, the inhibition is removed and information flows again and I change the eye in the new position, without anything in the middle (we only have the last image). This is called *saccadic suppression.*

Why does it not work when we push manyally the eye? In this case, there are no fibers from area 4 to the primary visual cortex, so the cortex is not informed of what we are doing with the hand.

We have seen the descending control of sensory afferences: al lalong sen-

sory pathways we have info from periphery to cerebral cortex, but also from upper centers to the thalamus, from dorsal horn to gracile and cuneate nuclei. The activity of sensory systems is always somehow modulaetd by upper structures: it is the mechanism that makes us percieve ous aims, concentrated. It is one of the mechansims for attention: when some path of cerebral cortex are active in one domain, there is a descending inhibition of other activities.

2.2.2 Blindsight

The superior colliculus has also a role in visual perception: blindsght happens when we have a lesion in V1, but in some cases the patient can still orient his eyes toward some kind of visual stimulus. The patient is blind but will guess if there is a light in the room and where. The person is not aware that it can see. According to the degree of damage of V1 we can have complete blindsight or something close to consciousness: this is because inf from superior colliculus goes to the thalamus but not to the LGN, but to the *pulvinar*, a huge nucleus on top and back of the thalamus, and sends info to the are 18 in front of the 17 (V1), and also 19, so the *association visual areas*, where we complete the visual perception. They give an enrichment of the information.

Chapter 3

Somestesia

Senses! We have 9 senses: touch, vision, smell, taste, pain, equilibrium, temperature, earing and proprioception.

In the touch system the enercy is a mechanical energy, and the transduction is the same in all sin receptors: the mechansism is the same for the spindle, so all mechanical receptors work this way. We stretch the memrbane and the channels open. These channels are large and both Na and K go across them $\longrightarrow$depolarization. We have different kind of receptors. One classification is: simple, complex and special.

- Simple receptors: the same neurons do all the job, transduction and coding of sensory information, so duration etc. We have free nerve endings which transduct the information

- Complex receptors: they work by themselves mostly like the simple ones, but they have something more to better codify teh stimulus, which is *conenctive tissue*

- Special receptors: the neuron cannot do all the job, so it can generate AP but cannot perform sensory transduction. These are ther receptors of the special senses, like vestibular system

The other classification: receptors are classified of 1st type, 2nd and 3rd.

- 1^{st} type: one neuron do all the job, so it comprises the simple and comlex receptors

- 2^{nd} type: need 2 cells to complete the transduction

- 3^{rd} type: need 3 cells the transduction, in the retina

3.1 Skin receptors

We have free nerve indings just superficially, not really sperficially because the outer layer of skin is continuously regenerated, there are stem cells that replicate and brings to the surface, where they die. Nerve endings terminate just below this region. Other receptors are of the 1st kind and have different connective structures in order to help the transduction, like *Pacini's receptor*, where we have a fiber ending covered by many layers of connective tissue. It is deep in the skin and it is responsible for what it is known as *deep touch*[1]. Messener, Ruffini and Merkel receptors detect the superficial touch, so the properties of a surface, the texture. With the deep touch we recognize the shape of the object because we need to increase a little bit the pressure.

While in the case of Pacini's body the connective tissue is very well organized, in the other case it is not a clear structure. Meissner receptors have a small receptive field, shile for deep receptros we have a higher receptive field. The important thing is that in the same region of skin we have all types of receptors: each of them will code some little different kind of information. Another classification: rapidly adapting or slow adapting.

- Slow adaptation: we apply a stimulus and he receptor will produce AP all along the time the stimulus is applied. The velocity of reduction of the response is what makes the difference.

- Rapid adaptation

Adaptation exists always.

In the skin this is particularly important: the majority are rapidly adaptive receptors. It seems to be evoltionary strategy not to have a cerebral cortex occupied by infomration which is not so important if it is constant information. Temperature, equilibrium, voloceptors, stretch receptors, receptors fro pH, CO2, O2 in blood, receptors which do not originate consciousness do not adapt. This is not done by cerebral cortex: it is the receptor itself which adapts, so it is a mechanism generated in the periphery.

(21.04.2016) The system works on he lipid tension: if we stretch the membrane, we reduce the barrier; We can have channels related to parts of the membrane and when we stretch the membrane, part of the receptor is open and we have the entrance of ions.

We have differet skin receptors with different connective tissue because these different connective tissues allows different kind of transduction. We stil lneed to open these channels. We have 4 main receptors in the part of

[1] We have superficial touch and deep touch

the skin where we do not have hairs. We have Merkel receptors, which are sensitive to compression and texture, properties of the surface.

Messener receptors are sensitive to the initial touching, so rapidly adapting receptor.

Ruffini receptors are sensitive to stretch: these receptors are important in the skin fro example when we move and it is a direct informaiton of the effectiveness of the movement we are doing.

Pacinian receptors are deep receptors, sensitve to *motion* of the skin and to *vibration*. Free nerve endings are nociceptive and where we have the hirs we have nerve endings around the radix of the hair, which are sensitive to the displacement of the hair itself.

Some of these receptors are more superficial and some other are deeper: those close to the surface are responsible for the capability to detect the properties of the surface, while the most deeper are responsible for the shape of the object. As a consequence of beeing more superficial or not, the receptive fields of these receptors are different. Receptive fields of surface receptors are smal land have quite distinguishible borders; receptive fields of more deep receptors have larger and less clear, less sharp borders, because we have to push more to activate those receptors.

How do they behave when they discharge? We have the same kind of stimulus, which arrives slowly and is maintained, and we have receptors which respond rapidly to the onset of the stimulus, then become silent. We have rapidly adapting receptors and slowly adapting receptors. The discharge almost is the same between RA1 and RA2 as well for SA1 and SA2: the distinction is just to link the response to the receptor. SA2 are Ruffini receptors, RA1 are messner receptors. R and S mean rapid adapting and slow adapting. All skin receptors are rapid adaptive receptors, so the slow one are relatively slow, the RA are more rapidly adaptive.

The fact of being RA or SA has also a % component: cilinder with peas on it, the cylinder moves (rotation) through the finger and you record the activity of the cortex. Every time we have a spike, we have a dot. This is the way blind people do read Braille. What reaches the cerebral cortex is the overall activity of all these receptors. In the same region of skin we have all these receptors.

When we apply stimulus, the depolarization of the membrane is known as *receptor potential*, the same as EPSP.

3.1.1 How are sensory stimuli coded?

We want to know location, intensity, duration, modality of the stimuli (which kind of energy). We prefer to detect onset and offset of the stimulation. If the

intesity of the stimulus change, the receptor discharge again. This implies a cognitive load, because for example we know we are dressed, but we do not know what we are wearing. Surely, we can detect very quickly if somehting changes.

For the coding of intesity: we have a stimulus of a certain amplitude which generate a receptor potential which will gie AP at a certain frequency. Higer the intesity of the stimulus, higher the frequency of the AP. So, we have a *conversion of intentity in frequency of discharge*. How does this conversion occur?

If the receptor potential increases, when the Vm during the AP is falling down, it will find the membrane depolarized before that when the intesity of the stimulus was less intesive, so another AP will arrive. There is a relative refractive period, so if the depolarization is high enough, we can generate another AP. We can code frequencies higher than the highest frequency of discharge of a sigle neuron: it is a case of *population activity*, the involvement of a population of neurons. How? If we apply a light stimulus like a pin on the skin, we will activate at the highest level the receptor just below the stimulus, but since the skin is elastic, we make a deformation all around and we have a certain degree of activation all around. If we increase the pressure with the pin, the deformation of the skin will be larger and more neurons will be involved. The cerebral cortex will understand that this pattern of activity (high frequncy of discharge in the center, lower in the periphery) into 2 ways: we can have also this patter with a larger stimulus than a pin. Our brain during the life understoood that the most frequent situation that produces this effect is the pin: it is a matter of learning. This is known as *population effect*.

Afferent neuron A: one synapse in CNS is never able to give AP in the postsynaptic neuron B(only in the muscle). In order to produce one AP, we need for example 2 synapses: AP in neuron A, will the neuron B discharge? In another neurons with which neuron A makes only one synapse (C), it will not discharge. What if we produce 2 AP in A? Neuron B will respond with 2 spike, becuase we have 2 AP and 2 synapse, so 2 AP in B. We have 4 releases of neurotransmitter. In C we also have a discharge, with one AP because there will be 2 releases. This is *temporal sumamtion*: the effect of the release summates in time.

We can also have spatial summation, for example if neuron C has another afferent neuron. If we apply the stimulus only in one afferent neuron, C will not discharge, even if only in the other neuron. If we apply a stimulus in both afferent neuron, C will discharge. The effects summates in space instead than in time: we summate in time when the pathway is the same, we summate in space when the pathways are different. We have few afferent fibers with

respect to the number of neurons we have, in this case, in the dorsal horn of spinal cord. One fiber will give many synapses to one neuron, the one closest to the fiber, but arborization of the axon will go around: this produces a pattern of activity in spinal cord which is different in intesity and number of fibers which are activated.

Another aspect now.Neuron C is in the subliminar zone of the first afferent neuron: it is excited, but not enought to produce an AP. To make it discharge, we have to increase the frequency of stimulation in the first afferent neuron.[2]

We have to insist on the properties of sensory neurons with the idea of receptive field.

3.2 Tactile acuity

We have a region of skin and the neuron which body is in the ganglion of the dorsal root. Its terminal branches receive information fro ma region of skin: if I apply a stimulus in that region of skin it will discharge. As we know, we have a problem: we have too many sensory fiber with respect to the size of the spinal cord, so we cannot maintain one-to-one progression of information, we need convergence when we enter in the spinal cord. Maybe 3 neurons converge on a single neuron, so the final receptive field of that neuron is as large as the sum of the receptive fields of the afferent neurons. Due to convergence, entering in the spinal cord and going along the neuronal pathway, receptive felds increase in size. All the sensory info from skin goes to spinal cord and then goes in the thalamus, in the posterior ventrolateral nuclei, which is smaller than the sum of the dorsal horn.

This is against what we wish, because we want a precise definition of location in space and increasing the size of receptive field, we loose this precision. So, we must invent something which can solve this problem: we do this based on the *lateral inhibition*, which happens all along all sensory pathways. We have a region of skin, apply stimulus, activate a neuron and the informaiton goes along the pathway: if we increase the pressure, we will recruit more and more neurons all around and they will discharge. In the cerebral cortex, there will be a central region of the cerebral cortex where we have a high frequency of discharge and a surrounding region where we have a decrease in discharge. In order to be sure that the stimulus was applied in that point, we have to discriminaate between the activity there and all around.

To have more, every neuron along the sensory pathway sends inhibitory collaterals to the surrounding neurons through interneurons. So, at the level

[2]Seen in the polisynaptic reflex, where we recruit more and more muscles.

of cerebral cortex, the discharge i nthe center will not change, but we will no longer have dischage all around. The intesity of discharge remain the same, but the contrast with respect to the surround is strongly increased $\longrightarrow$easier to detect the precise point where the stimulus is applied. Our systems prefere to work with *contrast* rather than intensity. Lateral inhibition is used to increase the contrast in order to solve the prolem of convergence. It is able to give again some kind of precision.

This is not enough: we cannot have the same precision everywere on our surface, as in the retina we have regions in our body where we have high density of neurons and regions in where we have lower density. Take a compass and try to apply the pins of the compass simoultaneously on 2 spots on the skin and see if we recognise the 2 pins or just one. This is the way in which the tactile acuity is measured: it means the less possible distance at which two points are recognized as separate. Which is our tactile acuity?

A-beta fibers enter the spinal cord, do not cross the midline, run in the gracile and cuneate fasciculi (cuneate brings information from the upper limb). The first relay is in the gralice cuneate; the seconf neuron cross the midline and go in the thalamus $\longrightarrow$medial lemniscal tract. The other pathway which originates from the skin is the one that brings indomrations about temperature, pain. The second neuron crosses the midline in the spinal cord and reahc the thalamus in the lateral-spinothalamic tract.

In the insular cortex there is the secondary sensory area. Primary sensory cortex: post-central gyrus.

Chapter 4

Cerebral cortex

6 layers. The first is the *molecular layer*: very few neurons but tangential fibers to the surface. They are fibers fro mthe neuron below which go to the first layer and spread a bit. In the fisrt layer, dendrites and axons communicate each other.

Then we have a granular layer, neurons are a bit larger. It is known as *external granular*. Then *esternal pyramidal*, in hwich neurons are pyramidal, then *internal granular*, *internal pyramidal* and *multiform layer*.

The external layers are mainly connected with other regions of the cerebral cortex: granule cells are often afferent neurons, while pyramidal cells are usually efferent neurons (both internal and external).The two external layers communicate with other region of the cerebral cortex, which are responsible of cortico-cortical connection, while internal layers are responsible for connection to other regions of the brain (thalamus, spinal cord). If I'm in the area 8 and I want to send infos to area 17, which kind of information I wish to send? Info for saccadic suppression. Which layer of area 17 will send info to area 17? The 3rd. Which layer of area 17 receives info from area 8? The external granular.

In a primary motor area which layer will be developed more? The internal pyramidal. The visual area (area 17), one of the most developed sensory area in our brain, which layer will have more developed? The 4th (internal granular). On these basis the different thickness of the cerebral cortex lead to the building ofaa map of the brain. It was difficult to atttribute different functions to different parts of the brain!

Broca= area 44. The frontal areas are important for the behavior. The primary motor cortex has a huge 5th layer and a small 4th. A big 4th layer is found in a part of cerebral cortex devoted to receive information, so sensory area. On the basis of the thichness of the layers, Broadmann made a classification of the cortex: he made slides and see the thickness and assigned

a number to each different configuration. Post-central gyrus has harea 3, 1, 2 (in this order!).

The suddivision of S1 area (primary snesory area) are 4: 3a, 3b, 1 and 2. In the cerebral cortex, the information from different receptors arise from different neurons. Different receptors arise in different regions of the cortex. From Merkel and Meissner receptor the information arrives into different *cortical columns* a cylinder of neurons which work the same region of space in the same way: we have a *segregate representation* of the information. These columns are 0.5 mm wide: there are a lot of neurons which have the receptive field in the skin, but RA vs SA activity. It was shown that we have *stripes* instead of columns if we look at them tangentially. Nowhere in the brain this segregated information is rebuild up. Understanding of environment done by simultaneous activity of all this pool of neurons, like an orchestra.

Information is elaborated by different neurons, there is a *segregation of the information*: that's why we have 4 somatosensory areas and we also have 4 different homunculi in that area. So, information is segregated not only in the same are but also between different areas. In the case of vision, we have more than 30 visual areas, each of them has its own representation of the retina and delas with different aspects of vision. This is the way which is used to code *location*, so how can we recognize where something arrives on our body. Thanks to the topography, to homunculus. When fibers enter the spinal cord, in the case of touch they enter at different levels of spinal cord depending on their origin: this separation is amintained all along the sensory patheeay until the cortex .

The 4th modality of the stimulus is which kind of energy made these neurons fire: this modality is coded by the fact that different sensory modalities reach the brain in different regions. If neurons fire in a certain region, their discharge originate from a certain stimulus. To recognize modalities, we need a dedicated region in the cerebral cortex and specialized sensory neurons. Neurons specialized for vision are perfect to detect light, not so good to detect touch. They could, but every receptor is built to better respond to some kind of energy, not to any kind of energy. Pressing with a pen to our closed eye, we see a ring of light, because our eye is round and when we push, we create a cone, because the pin goes inside. Receptors are mechanically compressed and they generate action potentials, because we depolarize them: we need more energy with respect to light, but we can make it. This AP go to area 17, so they are interpreted as visual experience. So, in order to detect the modality, we need specialized receptors but more than all dedicated regions i nthe cerebral cortex, because it is there that the experience is done.

(26.04.2016)

Why so many subdivisions for area S1? Monkeys in South america: "new

world monkeys", their brain is almost flat so it is easy to go into it with an electrode. In Africa, we have "old world monkeys". To map the receptive fields of the region posteriorly to the central sulcus: we have a complete scimmiunculus in area 1 and another one in area 3b. Different modalities originated from receptors in the skin are found in the same area, but segregated also btw different areas. All of them are primary areas and receive from the thalamus, so a huge 4th layer. Fibers from 3a to 3b: the 3rd layer. We have a gradient of projection form anterior most part or S1 (3a) to area 2. How the receptive field of area 3a are with respect to area 2? I expect to have a larger receptive field in area 2, because area 3a only receives projections from VPL of thalamus. 3b, 1 and 2 also receives infromation from the other areas of S1: receptive field will be larger and there is a certain degree of convergence.

Make lesions in the hand region of area 2 and ask the monkey to pick up pieces of food in a funnel. They made reversible lesion with *muscimol*, an agonist of GABA, which was then removed. The lesion was done in one emisphere and the controlateral hand was affected: the monkey started properly, but then was unable to really find and catch the piece of food. The monkey wasn't able to make the right movement of the hand, but the lesion was in a primary sensory area! How is it possible? The problem is *sensory-motor integration*: the motor system is not informed of the sensory properties from the periphery. Some information arrives, but it is not properly integrated with the motor output. Motion needs sensory information in order to be performed.

Deeply in the insula we have the primary taste area, while olfaction is inside the temporal lobe.

4.1 Overview of the cortex

THe cuneus is the medial view of the emispheres on occipital cortex: we recognize the calcarine fissure, also known as striate cortex. The 4th layer is huge and inside the 4th layer, which is grey matter, we have a stripe of white matter, fibers from the thalamus (that's why striate cortex). Cingulate cortex is responsible of pain and this is important because there are no nociceptor in the brain, but also no fotoreceptors, tactile receptors but we can evoke visual experience and somatosensory experiences. The reason it that the region where pain is formed is the cingulate cortex, which is deep in the brain: that's why the surgeon can touch the brain without pain, because the nociceptors are too deep inside. In S1 we have the representation of pain, the real modality of pain has its own receptors, which are free nerve endings,

so if we apply stimulus there, this is detected n S1. Pain can also change accoridng to envronemnt, *emotional state*: we can modulate pain without modulating sensory periphery. This emotional state is worked in cingulate cortex.

Cortical column We see different bign neurons, granule cells, dendrites that covers almost all the extent of the colums, then fibers in the first layers and other different layers of fibers.

4.2 Development of cerebral cortex

During the time after birth, we have an increase in number of connections, but the number of neurons is still the same. The head of the baby is large with respect to the rest of the body. Linphatic tissues increase at 10 years old. The head as a strong increase during the first years of life because we have an increase in the number glial cells, which grows 10 times more than the number at birth. This means that, at birth, the brain does not function that well: the neurons are the same, but conenctions are poor and the insulation of neurons one from the other is not so well done. Some animals are already wired at birth, while for use wiring does not proceed uniformely during the years. Wiring mainly depends on *myelination*. One of the first region in the brain which undergoes myelinization is the frontal cortex: important for communication because we have Broca area (language production), motor areas etc, so attention, communication and motor skills first.

Then from 7 to 5 years we have increase in myelinization in parietal and temporal cortex: this is the time in hwich we learn, improve linguistic abilities (because of the Wernicke area — comprehension of language), relation with space etc. Finally, at 16–20 years, we have the second and last myelinization at the level of frontal cortex again: this is when the maturation of a person is completed. Once the job is done, we are adult. This is important because in the frontal lobe we have different subregions which govern *behaviour*. We have in that region the inhibition of non-appropriate actions, emotion and meaning os sensation etc.

This does not mean that after 20 years the brain does not change: the brain is a highly dynamic structure. We have *synaptic plasticity*: LTP, LTD. Take a monkey and place it in front of a couple of boxes inside which there was some food (only in one of the 2 boxes). The monkey has to explore the surface of the boxes in which there was the food. The monkey learnt where the food was, then they made more difficult to recognize the box and the monkey became more skilled. Before doing this, they made a small hole in

the region of the hand and went to map the receptive field of the fingers and the tips of the fingers: after the experiment of disscrimination, they made the same recording of receptive field and the found an enlargement of the cortex in the region connected with the fingers. This means there was synaptic plasticity: the region of cortex which works more, increase its size. This does not means that the regions of the brain increase their size without any side effects: the region which increase its size make this at the expenses of the surrounding regions.

This is clear in the syndrome of the *phantom limb*. Sometimes it happnes that you don't have the forearm bit if you touch the remaining arm, the person will say that he feels you touching his hand. This happens also if you touch the head: the limb is not there but the subject can refer sensation about the limb which is no more there. In the homunculus of S1, the region of the heand does not receives anymore from the periphery, but the region is still there, so the hand area in the cortex is there, the hand is no longer there. It happens that fibers which goes to the face and to the arms will sprout in that region of the hand, so if you apply the stimulus to the face, the subject will feel as if you were touching the hand and the head. How wide is the region where I can have this sprouting? It was believed that you could not go far from the modality which was damaged, so that the sprouting occured only in that damaged area: this was supported by the believe that if you are blind, you become good with touch or acustic information $\longrightarrow$this can be done with training, not because of sprouting! With fMRI, we saw that if we train a blind people to touch, V1 will become active after tactile stimulation, not visual stimulation! How can you say when you see V1 active after tactile stimulation that the person is not imaging what he is touching? The person imagined, visualized what he was touching. There is still no clear point.

Primary areas are those that say what they do. If you make a lesion there, you have a clear deficit in that modality. If you apply stimuli, you evoke movememnt or perception in that domain. These areas cover a small amount of cerebral cortex, so what does all the other parts of the brain do? What about the frontal cortex, the parietal, temporal association cortices?

Occipital association cortex. The job is to recognize the information which arrives from the retina. The fact that we live in 3D space is a problem for our brain.

Temporal association cortex. Mainly visual area. The temporal association cortex is involved in recognition of object. Lesion studies in humans: *visual agnosia*, the difficulty in giving a name to objects. This could derive

from a vascular accident. If you ask the patient to drow the object, he does it, so he perfetly sees byt cannot give a name. Maybe the patient could describe the object. In animals, they tried to do something more elaborated: we have the spike activiy of neurons in temporal cortex when the animal (monkey) sees different images. We see that the neurons responds very well to some stimuli but not to some others, and the neurons can recognise some patterns of light but not some others.

The specialization of this part of the cortex is so deep that we could have problems in the recognition of faces.

Parietal association cortex. The anterior part of the parietal cortex is the *somatosensory cortex*. The posterior parietal cortes is subdivided by the intraparietal sulcus in a superior lobe and an inferior lobe. We have *vision related to extrapersonal space*, so where are things in space. We have different situations: if lesion in the right posterior parietal cortex (inferior lobe) brings to *visual neglect*. It means that the person ignores part of his visual space, and the part which is ignored is the controlateral one with respect to the lesion. This pathology appears when we have a lesion on the right. If the lesion is on the left, we develop *afasia* because of the Wernicke area. It means that the patiens ignores half of his visual field. Ask him to drow a clock and it will place the number only in the right half. It may be simply visual, but the parietal cortex is a *polisensory area*: quite frequently this patients ignore their body as well. The same is for acustic signals. This syndrome reduces in time.

A lesion in the superior parietal lobe is still associated with problems in vision and space, and what happens is known as *optic ataxia*, a difficulty in moving in space, so deals with moving in the extrapersonal space. To recognize this syndrome, I show a patiens a sheet with a hole in the middle and ask the patient to insert the hand in the hole. Then change the orientation of the sheet, the patient is unable to fit the orientation of the hand with the orientation of the hole. It will make mistake, but not if I ask to change the orientation of the hand while orienting the sheet: the problem arise when I ask him to move the hand in the space. The change of orientation is not a movement in space. The difficulty is in moving under visual guidance, so that if the patient closes his eyes, it will be able to do the right movement. How to calculate the distance of objects? I need *binocular vision*: we see a map of the visual enviroment which we build time by time. I can detedc the distance moving to the object.

So, inferior parieta cortex gives the cognition of the space around, the superior one gives the distance from me to the object. I have to move from

retinal coordinates to body coordinates to hand coordinates to move toward an object: after I've done these coordinates transfomration I send the infomation to spinal cord in order to move.

Frontal association cortex Like Phineas Gage. After 10 years he improved, got a job again! Before this, there were no clear ideas of the job performed by frontal cortex. The frontal lobe is critical for our ability to interact with people, to build a social life and to understand the consequences of my actions. Morality equity, honesty are worked by frontal cotex. The central sulcus is central in humans but not in animals, in which it is more anterior: the frontal lobe is important for the human behaviour. The difference is in the amount of frontal lobe we have, not from the qualitative point of view. The difference is from the quatitative point of view.

Why until now the surgeon choose the frontal cortex to go deep inside the brain? Because the damages are not so bad. So, problems in frontal cortex are associated with *repetitive behaviours* and *utilization behaviour*. This is when the patient cannot stop his behaviour: if something is on the desk, the patient has to touch everything.

(28.04.2016)

4.3 A little review

In monosynaptic reflex there is already a sort of integration: we can try to inhibit the reflex or exagerate it, because the α-motorneuron is the last pathway of everything: receives infos from descending pathways, pyramidal system and reticular-spinal system.

In the cortex, we have area 1 (somatosensory), area 2 (somatosensory), area 3 (somatosensory): these are behind the central sulcus, in the postcentral gyrus. Area 4 is the primary motor area, in front of the 3a. Area 5 is behind the area 2 in intraparietal cortex and it is the associative area. Area 6 is the premotor area in front of area 4. Area 7 is behind area 5 in posterior parietal cortex: 5 and 7 are the superior parietal labule. Lesion in that region affect the integration btw visual system and motor output (optic ataxia).

Area 8 is the frontal eye field, in front of area 6 in frontal cortex, for voluntary eye movements (saccads); I do saccads also for other purpose, like the *orienting reflex*. Area 17 is in the occipital cortex, it is the primary visual cortex: a small part is on the outer surface of the brain, the rest is inside the interemispheric fissure. Area 18 and 19 are visual associative areas on both sides of area 18.

Chapter 5

Movements

Voluntary movement means conscious movement, purposeful movement. We saw them by several points of view, now another one. We have a leat 5 different kinds of movements:

- Reflex movements: fast, quick and stereotyped respones, becuase the circuitry is very simple. All of the reflexes are typical for the response we have. They are typically graduated by the intensity stimulation that evokes them. The idea is that the reflex organization of the spinal cord is stereotyped, but the cerebral ortex will play on this simple mechanism to have a more complex behaviour.

- Saccadic movement: typical of the eye. It does not mean that we do not perform fast movements with other parts of the body, it's just not a saccad. In both cases you decied when to do the movement, where to direct the eye or the hand and the velocity, but when the movement start there is not an on-going control, they are phasic movements. The organization is complex and subcortical (brainstem)

- Postural movements: they require activation of many muscles and depend on sensory informations. It is the job of the spindle. In order to fight against gravity we need to recruit a large number of muscles and they strictly depend on *sensory information*, which is not needed for saccadic eye movement but in the beginning of the movement.

- Rhythmic movements: walking is a rhythmic movement and it is based on a reflex organization. They are a combination of voluntary and reflex movement: when we walk, we decide when to start, the velocity, when to stop, but during walking we don't think about what we are doing. The onset is voluntary and the prosecution is reflex

- Voluntary movements: directed to a purpose and lerned. They improve with practice. They need a more complicated circuitry.

Movements undergo 2 types of control:

- Phasic: temporary activation to perform discrete movement (like catch a fly). Fast movements where the control has to be done in advance with respect to the movement

- Tonic: activation maintained over time to stabilize joints

Motor control needs sensory information: it is as more critical are the lower the hierarchical level is (reflexes). there are at least 3 models that illustate the role of sensory information in motor control:

- Open loop

- Feedback

- Feedforward

Feedback Plan a movement: the infromatio is sent to a system, the *comparator*, which sends informations to the effector, which makes the movement. Btw effector and movement there are sensors, which give a feedback signal to a comparator, which time by time compares the information avout the designed movement with the information of what is actually going on. All the time we perfor me tomvement, we continuosly check how it is going on and we can also change the signal. For these reasons, it is slow. The best comparator is the *cerebellum*.

The comparator calculates the differences btw the designas movement and the one produced. If the 2 values are different, it generates a signal that changes the effectoractivity. These systems are accurate and efficient and are useful to maintain a variable, as it is the case of the control of posture. They have the defect to be slow, because the efficiency depends on feedback form the periphery and a sudden postural change may not be adequately compensated, because it takes time.

To find a solution for sudden changes, I need to have a system that accomplish for this: this helps me to maintain posture even in the presence of fast stimuli, *stretch reflex*.

Open loop The controller will drive the effector and we have the movement. During the developmen of the movement, the sensory input is completely ignored: the motor commands are structured from the beginning and do not take into account the effects they can have. It is a system whih privileges speed over efficiency. Balistic (saccadic)[1] movements cannot be modified on the basis of sensory information (catch a fly, catch a fast ball). Before, when we plan the movement, we take into account the sensory information.

Feedforward A priori control. The movement is as it was before, but we anticipate a possible sensory change in the environment. In the case of balistic movement, we decide that the target will not change; in this case, we know by sure that changes in the target position will happen. We still have the desired movement, the controller, the effector and the movement, but the controller takes into account sensory information *in advance*. It is quick, more fast than feedback (because it has not a comparator and does not depend on sensory information) but needs time to learn to be effective. Availavle sensory information has to be valuated as well as the consequences, on it, of the movements that will be performed. Free climbing, taking a curve at high speed (better in videogames).

For example, a videogame in which we have to drive a car, the good ones understand how the curve is, so they change direction before, they are able to anticipate, but they have to learn how the sensory information will change. Anatomically, the controller is the *cerebral cortex*.

5.1 Motor equivalence

It is the ability of different motor system to achieve the same behavior. If we try to write with different parts of the body, the writing deteriorates but the same letters are always done in the same way, independently on the effector: the motor programs can be executed independently from the effector. Movement does not depend on the effector we use, it is somewhere in the brain: the fact that the movement is done more or less well depends on the training of the effector. The behavior is based on our own representation.

The sensory system is the opposite: it builds a representation of the world on the basis on what there is in the periphery. This is the idea of motor equivalence: every movement can be done with every effector, because the movements are planned.

[1] For eyes we say sacacdic, for the rest of the body we say balistic movement.

5.2 Overall organization of motor systems

Motor systems are organizes hierarchically (3 levels) and in parallel. The three levels are the spinal level, the brainstem with cerebellum and the diencefalon and cerebral cortex. The motor areas of cerebral cortex may affect spinal cord both directly and through the brainstem. In early vertebrates we only have the spinal cord, then structures were added (brainstem and cerebral cortex): nothing was changed in the oldest one, only new features were added. When the control became more and more complicated, the structures which appeared did not change, they added informations.

We have motor areas, which sends information directly to spinal cord and information by way of other structures, so a slower indirect way to influence spinal cord. The three levels receive sensory information and are under influence of cerebellum and basal ganglia, both acting on the erebral cortex via the thalamus. They do not directly send information to spinal cord. The motor cortex determines which motor groups are activated and the amount to ferce to exert. Based on input fro mthe motor cortex, the basal canglia, cerebellum, brainstem nuclei and spinal cord initiate appropriate muscle contraction to accomplish appropriate and porpuseful movements.

5.2.1 Pyramidal tract

It is a bundle of fibers forming the pyramids in the bulb. In the medulla oblongata we have a decussation of these fibers: 2/3 cross the midline and we find them in the lateral column in the pspinal cord, 1/3 do not cross immedialty but after, when they have to reach the anterior horn is spinal cord.

The pyramidal tract arrives to interneurons and α-motorneurons: in all animals the pyrmaidal tract reaches the anterior horn but not directly the α-motorneuron, because it reaches first interneurons. There is an exception: is some particular cases we have a direct input from α-motorneurons, only for the α-motorneurons of the *hand*, mainly in primates and small animals which use the hands to eat. It is as if the cerebral cortex decided to have the best control working directly on the hand.

Pyramidal tract originates from a wide portion of thecortex, from a huge ensemble of areas around the central sulcus, but those fibers which goes directly to motorneuons originates only form area 4 (primary motor cortex). Area 4 pathways goes both to interneurons and motorneurons; area 6 sendos again to structures below; area 3, 2 and 1 also sends informations. Fibers which are aprt ofthe pyramidal tract not only go to motorneurons but also to the dorsal horn, in particualr fibers from 3, 2, 1 and parietal association

areas. This is surprising: it is to *control sensory input*. We control sensory input all the time, we saw a huge example with saccadic suppression: the cerebral cortex exert a strong influence on the thalamus. We can make a lesion in monkey's pyramidal tract: difficulties in doing the task of grasping, but the precision of the movement of the hand is compromised.

5.2.2 Pathways to motorneurons

We have the cerebral cortex in yellow with area 4 and 6, then the system of fibers which goes to spinal cord. It can go to the *lateral system* and the *ventromedial system*.

Lateral pathway is involved in voluntary movement which involve distal muscle. We have a dedicated control to these muscles for example in the independence of the fingers. This voluntary control depends on the direct controls of the cortex. The lateral pathway is involved in voluntary movement of distal muscles (independence of the fingers) and depends on the distal control of the cortex. Rubro-spinal tract in humans is underdeveloped, but ir can substitute the functions of the cortico-spinal tract. The red nucleus was investigated in the cats, because the size of the head of the cat is almost the same in every cat. It receives directly connections fro mspinal cord and sends fibers to the alpha-motorneurons. When we have a lesion of pyramidal fibers, the rubro-spinal tract may take part of the functions of the pyramidal fibers (while normally it has few fibers and not mich functions).

The *ventromedial pathway* uses sensory information on balance, body position and visual environment to maintain balance and posture. We have reticular formation[2] and collicolo-superior and vestibular nuclei. These two structures are controlled by descending system from pyramidal system. We have 4 vestibular nuclei per each part: superior, inferior, medial, lateral. Superior, inferior and medial are the homologous of spinal cord because they receive information from the vestibular receptors utricule and saccule. In this case, we are talking about the lateral vestibular nucleus, from which it originates the vestibular-spinal tract; it also receives fibers form the cerebral cortex as the superior colliculus (orienting reflex) and the cerebral cortex still maintains its control.

We have the *motor homunculus* in the primary motor cortex, firstly drawed by Panfield. Panfield did those experiments because it was already known from animals that there was a motor representation of the body in the cortex. He was a neurosurgeon: he opened the skull and applyed stimuli to see if the patient moved some parts of the body. Since in somatosensory area

[2]See di-synaptic reflex and Sherrington's experiment.

we have receptive fields represented, in motor cortex we have motor units represented. It is not so: they found that different muscles are represented in the same region of cortex. It means that there is not a so precise representation, but a multiple representation of muscles, so the homunculus is not so precise. If we accept that there is a representation fo the movement, we accept also that stimulating that point we can activate more muscles. The flection of the finger for example: we can make that movement for different reasons and for different kinds of movements. These movements are differently represented in cortex, so *simple movements* (one joint movements) are represented in the motor cortex, not the motor units.

5.3 Corticalization of spinal circuitry

Some neurons in primary motor cortex receives proprioceptive input from the same muscles upon which they act, while other receive information from the area of the skin that is stimulated by the contraction of these muscles. In the spinal cord, we have alpha-motorneurons which drive the muscle and thim make some kind of movements; the same motorneurons receives infos from the spindle and from the skin. The motor cortex does the same job: the same information which comes from spindle to the motorneuron goes to the cortex. The cerebral cortex maintain the organization adding neurons, integration, complexity: we still find the same orgnaization that we find in the spinal cord.

5.3.1 Descending pathways: corticofugal fibers

Is this the brain of an old world monkey or a new world monkey? Old world monkey, because it has sulci and fissures. We see location of corticospinal neurons, corticobulbar neurons and both. We see how wide is the region of the brain that sends info to spinal cord: we have a great intensity in M1 in front of central sulcus, but also from the postentral gyrus to the superior lobus, also from temporal and prefrontal cortex. These neurons in M1 sends informations to anterior horns.

5.3.2 Peri-rolandic areas of cerebral cortex

Broadmann classified all the regions in front of area 4 are *area 6*. Other people found that there were differences and subdivided area 6 into three regions: they are the *supplementary motor area*, which is medial, then the *dorsal premotor area* and *ventral premotor area*. these 3 regions were further

subdivided into a rostral and a caudal part: caudal supplementary motor area maintained the name SMA, while the rostral one is the pre-SMA; then caudal dorsal premotor area and rostral dorsal premotor area; then premotor ventral caudal and premotor ventral rostral.[3]

So, we have SMA and PM. PM is subdivided in dPM and vPM. SMA is subdivided in SMA and pre-SMA. PMd is subdivided in PMdc and PMdr. PMv is subdivided in PMvc and PMvr.

Representation are dynamic everywhere. Single areas in premotor cortex are linked to single areas in parietal cortex. MIP is connected to PMv. For some reason, the central sulcus came and separate the primary motor and the primary supplementary area, even if they are strongly connected.

F1 is M1 in the Rizzolatti nomenclature. M1 has a somatotopic organization: movements are encoded by populations of neurons; the activity of these neurons encodes for the amount of force and the direction of the movement. Knowing where the object is is noth enough: we need to kow also the position of our libs with respect to the object. This is achieved by PE area, a sensory area.

Then we have the SMA (F3) and pre-SMA (F6): they appear in the surface of the brain, both of them receives infos from prefrontal cortex but also from parietal cortex. They are motor areas, somatotopic orgnaization. In premotor area we have the representation of the trunk: SMA is important for posture and to control posture we have to control the trunk. Main connection in an area in the parietal cortex which is the *secondaru sensory area* S2: it has a bilateral representation of the trunk, brought to the SMA for motor control. F3 has main parietal connection with Peci forpostral information. F6 has poor parietal connetion, prevelent with prefrontal areas.

Then we have PMd (F2, anterior, and F7, posterior). One of them is somatotopic. They have connections woth parietal cortex for limb movements. PArietal connections also to reaching movements; I also have to maintain the infos of the location of the object, so if I ask the animal to reach and grasp and touch a spot of light, the neurons of PGm will respond. Another area, lateral F7 is for supplementary eye fields (area 8) receives infos about the position of the eyes during exploration eye movements, which is important because objects fall on different positions of the retina.

5.3.3 Premotor dorsal cortex

For working memory. The monkey is facing buttons and will be rewarded when she will press the proper button when the adjacent led will flash. The

[3]Then the group of Rizzolati used another nomenclature, F1, F2 etc. We won't use it.

monkey has to wait a while before pressing: when the monkey sees the stimulus, the neurons discharge and then, when the monkey pushes the button, we have the disappearance of the stimulus. This is strange: neurons in motor area which discharge when the monkey is steady and do not discharge when the monkey is moving. The neurons decide which programs of the movement is going to be done: this is because working memory: when the information has reached the cortex, there is no reason to discharge.

5.3.4 Motor cortex and fronto-parietal system

F2 is the rostral part, while F2 the caudal. If we apply a stimulus to F4, we have a complex movement, a *multijoint movement*. Parietal conenctions are with areas which contributes to the transformation of position of the objects in space in movements to reach them.

5.3.5 Premotor ventral cortex

We have *mirror neurons*: working on monkeys of premotor cortex. They found neurons that discharge in a similar way when the monkey perform the action and when it sees the action to be performed by someone else. They called these neurons mirror neurons. They are important for empathy and communication. In humans there is no demonstration of existence of these neurons, becuse we cannot insert an electrode, but with MRI they found that the Broca area behaves like mirror neurons do, so if I ask someone to take something in MRI machine the area comes on, and also if the person sees the action from someone else. The mirror area in himans corresponds to Broca (44 and 45), but in monkeys there is not area 44 and 45. Mirror neurons are an old system which might be importat to understand what other people does, so I can start a communication with this person.

The involvement of each of these areas in the planning and execution of movements depends not only on the properties of its neurons, but also on the context in which the movement itself is carried out(ex. mirror neurons). From this point of view, the cerebral cortes seems to be involved more in the cognitive aspects ogf movement than in its real generation.

5.3.6 Functional streams: the parieto-frontal system

(3.05.2016)

It plays a crucial role in composition of motor commands, selection of conflicting motor plans and in the change of motor trajectory. Single parietal areas are connected to single premotor areas: each of these connections

seems to be devoted to deal with saccads, arm coordination, representation of action.

The motor analysis of object is different from the visual analysis of objects. We need vision in order to make a proper analysis, because motion and vision are worked separately in the brain, they are analized differently.

manca esperimento scimmia

In the second case, the handmark was close to the food: then lesion in superior parietal lobe of parietal cortex. The monkey was unable to recognize the position of the object. There are so functional streams, dorsal or ventral, indicating flow of information from one area to another one. The dorsal is responsible of recognition of position in space, the ventral for what the object is. Now, the dorsal stream is named *for action* and the ventral *for perception*.

Both streams are activated: when we receive visual info, we don't know wheter we interact with something known or not. This is the classical definition, but information proceedes to the frontal lobe: V1 ventral stream to the frontotemporal cortex... If we want to grasp something, we can do it in a fast way (dorsal stream, faster than the ventral). We use dorsal stream when somehting drops and we quickly catch it. Information not only goes to premotor cortex, but also to the *prefrontal cortex*, which is the cortex in front of premotor cortex. Area in the same region are strongly interconnected.

There are different streams for the 2 main motor acts that we perform, *reaching* and *grasping*. For reaching, we need a complex system of coordinates, starting from retina coordinates. We have to move from retinal coordinates to egocentric coordinates: if we want to reach in order to grasp, those coordinates must become hand centered coordinates. Once the hand is addressed in that position, we do not longer need spatial coordinates. With grasping, we only work on the hand; with reaching, we work on the arm and body.

In reaching, eevrything is mediated by prefrontal cortex. In grasping, things are simpler: the info to dorsal cortex, to a vetral region in intraparietal sulcus, then F5 and F1.

The prefrontal cortex is something like a light traffic: it will tell to do that motor act, because it is correct, ethical, honest. All the information converge on the premotor cortex and stays there, but only if the prefrontal cortex will allow it.

How mich time does it takes to perform all these connections? 20–40 ms to have a response in the retina, then from retina we go to LGN (50 ms) and fro mthere to V1, and V1 neurons fire at a latency of about 40–60 ms. from V1 to V4 and parietal temporal area (70–90 ms), then prefrontal cortex, premotor cortex and to motorneurons and finally we perform the movement. The reaction time to a vey simple movement is less than 200 ms. This is

for the slow stram (ventral stream). At the end, 250 ms is the latency of a movement: it is the time that the brain takes to process simple visual properties and tell to start the movement.

Chapter 6

Basal ganglia and Cerebellum

6.1 Basal ganglia

Basal ganglia receives info from cerebral cortex, send to nucleus ventralis lateralis VLo for thalamus and back to motor areas and premotor areas.

Basal ganglia are involved in at leat 4 different cognitive funtion: supplementary motor area, premotor area and M1 are involved, fibers go to basal ganglia; we also have oculomotor function, direction of gates: the areas involved are frontal eye field (area 8) and supplementary eye field; then we have prefrontal areas which project to basal ganglia and are involved in associative functions and *executive functions*. There is also another region of the basal ganglia which is connected to limbic system, a colleciton of areas which are deep in the brain but they are strongly involved in emotion and motivation. Motivation and emotion are strong components for movements.

Basal ganglia have segment sections which mainly take care of different functions, which are related to execution of movement. Inside this amount of conections, we have 2 pathways which are mainly involved in the motor aspect, which is the easiest to be studied. We have the direct pathway and the indirect pathway.

6.1.1 Direct pathway

We have cerebral cortex which acts on putament and the drive is an excitatory one. The putament inhibits the internal part of globus pallidus which inhibits the thalamus. We have an inhibition of a structure which inhibits $\longrightarrow$disinhibition, so *facilitation*: the thalamus is no longer inhibited and can discharge upon cerebral cortex, so we can start the movement properly. This pathway is tought to be important to *facilitate the movement.*

Substabtia nigra acts on the putamen and drive the putamen: putament is disomogeneous, it has excitatory transmitter and inhibitory transmitter. SN potentiates its activity, independently if it is excitatory or inhibitory. If a damage in SN of more than 70% of the neurons, this drive decreases: putamen reduces its action of GP, so the circuit does no longer work. We have difficulty in starting the movement: in Parkinson's syndrome we have a reduction of movements that we normally can perform. Spontaneous movements are reduced and onset of movements is more difficult.

6.1.2 Indirect pathway

From cortex to thalamus to cortex: we have action on putamen which inhibits the external part of globus pallidus, which inhibits the subtalamic nucleus. We have again the inhibition of an inhibition, so subthalamic nucleus is facilitated when this pathway is activated. It facilitates the internal part of globus pallidus, which inhibits the thalamus $\longrightarrow$reduced drive on cortex. this is a parallel pathway with respect to the direct one: they are different neurons, involved in controlling the *unwilled movements*, those movements we don't want to perform.

A damage in SN, acting on putament, is responsible for tremor. We can solve the problem bu adding dopamine, applying deep brain stimulation.

6.2 Cerebellum

Cerebellum receives infos from all the cortex, sends info to VLc and still to cortex. The main input to the BG is from the cerebral cortex, a very strong input to the cerebellum comes from the *periphery*, mainly from proprioceptors through the spino-cerebellum pathways, but also form vestibular nuclei, visual cortex, acustic cortex, somatosensory cortex. All these sensory informations are concerned with *development of the movement.*

The cerebellum acts both on brainstem and motor areas, which project to the spinal cord: it does not control directly the spinal cord. It also sends infos to the reticualr formation; beside the lateral vestibular nucleus to control posture, the main output of the cerebellum is toward thalamus and cerebral cortex. Damages involve tramor, difficulty in terminating movement etc.

A lesion in cerebellum does not cause paralysis, but *ataxia*: difficulty in performing a movement. We have seen the optic ataxia: difficulty to address the hand to visual target, which happens in the superior temporal lobe (in inferior one, we have neglect). Range of movement errors: the movement is dismetric, we do not calculate exactly the distance of the object with

respect to our hand. We overextimate the locaiton of the object and we have difficulties in trajectory and performing oscillatory movements.

Crb is connected to brainstam by 3 peduncles: through the inferior one we have proprioceptive and vestibular information form spinal cord; medial ones receives fiers which originate in the postine nuclei, which receive information form cerebral cortex (cortico-cerebellar pathway form almos all the cerebral cortex). Through this pathway the cerebellum is informed of what movement the cortex is going to perform. Then the superior pathway, the efferent pathway for cerebral cortex, which goes to premotor and motor areas: the cerebellum suggest to motor cortex the proper program to execute the movement.

Crb is involved in movements which are performed agains gravity: for example, going by bicycle $\longrightarrow$crb suggest a series of movements. The cerebellum wil lstore that program in the cerebral circuitry and it will never be forgotten. The strongest memory we have is the *motor memory*. Cerebellum also work to support distal movements.

revise all the cerebellum anatomy

Parallel fibers have a common discharge, whicle climbing fibers have complex discharge. Purkinje cells have the highest frequency of discharge in the brain and inhibit the deep cerebrellar nuclei. These nuclei are driven by afferent fibers and inhibited by the result of the elaboration of afferent informations performed by Purkinje cells.