Recent insights in Pain theories & Relevant developments for Physical Therapy

In the context of patients with chronic unexplained pain

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Introduction

A lot of things occur in the brain, including things that happen without even noticing it. A lot of systems work together, to create a homeostatic and harmonious body condition. Which means the body should be balanced and healthy. However these systems don’t always work correctly, which results in a various number of symptoms. For instance sensations of pain, tingling and even non existing body parts.
This review describes three different brain systems and the consequences of their dysfunctions. The systems are:
- Mirror Neuron System
- Body maps, plasticity and their connection with emotions
- Innate Immunity theory
The authors hope to give the reader a clearer image of how chronic unexplained pain can be explained. Additionally, the authors will give the reader a glimpse of what future techniques have to offer for these kind of unexplained problems in physical therapy.

But what are chronic unexplained pain problems?
Chronic pain is pain that persists for an extended period time (for 3-6 months), and that is interfering with the quality of life. Chronic pain lasts despite treatment of its underlying cause. It can be a result of a long-term illness, or a lingering result of an injury. Unexplained pain means that the pain that persists is medically unexplained.

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Chapter 1.
Mirror Neuron System and its connection with pain

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1.1 Introduction

When someone yawns, you yawn. When you see someone scratch their forehead, you may feel an itch on your own forehead. When you see someone being afraid, you feel a visceral flutter of fear. How is it possible that you can experience all these feelings of others? Is the feeling that is occurring in your body reality, or does your brain fool you into a certain way?

One of the most exciting events in neurosciences over the past few years, has been the discovery of a mechanism that unifies action perception and action execution. The first preliminary report on these mirror neurons was published by G. di Pellegrin et al. in the study: “Understanding motor events: a neurophysiological study” from 1992. They found that one of the fundamental functions of the premotor cortex is that of retrieving appropriate motor acts in response to sensory stimuli. They concluded that it appears that hand-object interactions belong to those categories of complex stimuli which, like faces, are explicitly coded by individual neurons. These individual neurons were later called: mirror neurons. ¹

In this Chapter the essence of mirror neurons is discussed. Mirror neurons occur in many brain regions, these places all have different functions. It will be explained how the mirror neuron circuit works, and how dysfunctions in the different areas can eventually cause disorders.
1.2 Essence of mirror neurons

The mirror neuron system is a mechanism that unifies action perception and action execution. The essence of this ‘mirror’ mechanism is as follows:

- Whenever individuals observe an action being done by someone else, a set of neurons that code for that action is activated in the observers motor system
- Mirror neurons fire both when an individual performs a motor act, and when the individual watches another individual performing that motor act.

In humans frontal and parietal brain areas (frontoparietal system) possess mirror properties (figure 4).

The parietal and frontal areas are robustly and reciprocally connected, whereas having weaker anatomic connections with other parietal and frontal areas. Parietal areas provide visual and somatosensory input to frontal areas.

- The human inferior frontal mirror neuron area seems to be more concerned with action goals during imitation
- The human inferior parietal mirror neuron (touch and movement) area seems to be more concerned with the motoric aspects of the action to be imitated.

Figure 4
1.3 Location of mirror neurons

The frontoparietal system is composed of:
- The ventral premotor cortex (area F5) → frontal
- The anterior intraparietal area → parietal

A large number of studies showed that the observation of actions done by others activates in humans a complex network formed by occipital, temporal, and parietal visual areas, and two cortical regions whose function is fundamentally or predominantly motor. These two last regions are:

1. **Ventral premotor cortex (PMC)/ Inferior frontal gyrus (IFG):** in the bank of the arcuate sulcus (F5ab).
2. **The inferior parietal lobule (IPL):** on the convexity behind the sulcus (F5c) (F5c), is connected with rostral inferior parietal areas PF and PFG. These regions form the core of the human mirror-neuron system (Figure 5).

Other researchers have found mirror neurons in other sectors of the cortex:

3. **Insula**
4. **Cingulate cortex**
5. **Secondary somatosensory cortex**

The human mirror neuron system is linked with higher-order visual areas along the **superior temporal sulcus (STS).** The STS is located above the ear toward the back of the head (Figure 6). In this circuit, the STS would provide a higher-order visual description of the action to be imitated. The neurons in the STS are dedicated to detecting biological motion. For example: is that thing moving in the bushes a creature or a shadow?
1.3 Functions

1.3.1 Brain regions
Before explaining how the mirror neurons function and the mirror neuron circuit works, it is important to understand what the functions of the different brain regions are. In this way the circuit is better understood and the link to mirror neuron disorders is easier to make.

Function of the Ventral premotor cortex (PMC)/ Inferior frontal gyrus (IFG)
The PMC has motor and cognitive functions. The cognitive functions include space perception, action understanding and imitation.\(^{14}\) It lies within Broca's area, an important language area.\(^{15}\)

Function of the inferior parietal lobule (IPL)
The IPL codes motor acts (such as grasping) in a specific way according to the action in which they are embedded. This particular motor organization appears to provide a neural mechanism for higher order cognitive motor functions, including understanding of intention. These functions are represented in areas of the inferior parietal lobule, where visual information from both the dorsal and the ventral stream is integrated with motor information.\(^{16}\)

Function of the Insula
This network, including the amygdale, could provide the ability to empathize with others through the representation and ‘inner imitation’ of the actions.\(^{17}\) By observation and imitation of facial expressions the insula is activated. Activation of the insula results in feeling emotions. Feeling emotions is due to the activation of circuits that mediate the corresponding viscero-motor responses.\(^{18}\)

Function of the Cingulate cortex
The cingulated cortex is activated with the insula when people feel or observe emotions in others, caused by disgusting stimuli or stimuli representing pain.\(^{19}\)

Function of the Secondary somatosensory cortex
SI receives input from skin and forms touch maps.\(^{20}\) SII helps transforming specific positions in the space around individuals (peripersonal space) into arm, neck, and face/mouth movements. This circuit is also involved in space perception. For more information see Chapter 2.\(^{21}\)

1.3.2 Mirror neurons
The functions mediated by the mirror neurons depend on the anatomy and physiological properties of the circuit in which these neurons are located. Actions studied in the early mirror-neuron studies were actions devoid of emotional content. Accordingly, activations were found in circuits related to motor action control (parieto-premotor circuits).\(^{22}\)

The mirror neuron system (MNS) and its functions:
- The MNS fires if the individual is performing actions.
The MNS fires during observation of another individual performing those actions (with slightly weaker discharge compared with motor execution). The MNS provides a particularly efficient way to establish links between the observed action and other actions with which it is functionally related. Because of this establishment the MNS has a role in the ability to understand the intentions behind the actions of others. This makes someone be able to predict and understand what will be the individual next motor act, even if the next action of other people isn’t completely visible.

The MNS is linked with language. It is also located in Broca’s area, which is involved in language processing and speech production. The MNS fires at the sound associated with an action, this suggests mirror neurons provide a multimodal, fairly abstract coding of the actions of other people.

The MNS is shaped by visual experience, and thus may be critical for imitative learning because of the acquired tool-use properties. The MNS implements a simulation-based form of understanding other people’s mental states.

The MNS is helping us in understanding and possibly feeling the emotions of others by simulating their facial expressions. Hereby it is linked with empathy.

1.3.3 Categories

Mirror neurons are divided in two main categories:

1. **Strictly congruent** mirror neurons, about one third of all mirror neurons, fire for exactly the same action, either executed or observed.

2. **Broadly congruent** mirror neurons represents approximately two thirds of all mirror neurons and fire for actions that are either logically related (such as grasping and bringing to the mouth) or that achieve the same goal.

Outnumbering strictly congruent mirror neurons suggests that:

- Mirror neurons are not simply concerned with mirroring others, but they rather facilitate social interactions in which individuals often perform complementary actions to achieve a common goal.
1.4 The Mirror-Neuron Circuit

Neurons responding to the observation of actions done by others are present not only in area F5. A region in which neurons with these properties have been described is the cortex of the superior temporal sulcus. Movements effective in eliciting neuron responses in this region are walking, turning the head, bending the torso, and moving the arms. A small set of STS neurons discharge also during the observation of goal-directed hand movements.

If one compares the functional properties of STS and F5 neurons, two points emerge. First, STS appears to code a much larger number of movements than F5. This may be ascribed, however, to the fact that STS output reaches, albeit indirectly (see below), the whole ventral premotor region and not only F5. Second, STS neurons do not appear to be endowed with motor properties.

Another cortical area where mirror neurons are found, is a specific part of the inferior parietal lobule. It receives input from STS and sends an important output to the ventral premotor cortex including area F5.

In conclusion, the cortical mirror-neuron circuit is formed by two main regions:
- the ventral premotor cortex (area F5)
- the rostral part of the inferior parietal lobule

STS is strictly related to it but, lacking motor properties, cannot be considered part of it. 28

Below the mirror neuron circuit is presented in a simplified way.

<table>
<thead>
<tr>
<th>Performing action</th>
<th>Observating action</th>
<th>Action related sound</th>
<th>Motor response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frontal and parietal</td>
<td>Mirror neurons fire</td>
<td>No motor response</td>
</tr>
</tbody>
</table>

STS

(Provides and codes a higher-order visual description of the action)

If there is a deficit in mirror neurons the circuit doesn’t work correctly, this can cause several dysfunctions. These dysfunctions are discussed in the next paragraph.
1.5 Dysfunctions of mirror neurons

1.5.1 Symptoms of Mirror-Neuron System dysfunctions

In short, functions of mirror neurons are:

- Understanding and interpreting actions of others
- Learning from new skills by imitation
- Understanding the underlying intentions, thoughts and feelings that motivated the observed action
- Empathy
- Language recruitment

If the mirror neuron system doesn’t work correctly, it can be harder for the individual to carry out the actions described above. If there are deficits in the mirror neuron system, the symptoms depend on the location of the deficit. ²⁹

Given the physiological properties of mirror neurons, the links between the human mirror neuron system and imitation, and the key role of imitation in social cognition, it is highly plausible that dysfunctions of the mirror neuron system could lead to deficits in social behavior. ³⁰

1.5.2 Autism

It has been proposed that a core deficit of autism, a socially isolating disorder, originates from a mirror neuron system dysfunction. A disruption of mirror neuron system activity would preclude experiential understanding of others, leading to the social deficits of autism. ³¹

1.5.3 Echopraxia

The observation of actions done by others leads to the coding of potential motor acts in the parietal and premotor mirror areas by means of the mirror mechanism. These potential motor acts typically do not determine overt movements in the healthy adult brain because the manifestation of these acts is suppressed by the frontal lobe. Damage to this lobe would destroy this control mechanism, thereby transforming the potential motor acts into actual motor behavior.

Echopraxia is a term that describes forced and uncritical imitation of behaviors. The exogenously triggered behavior is sustained through endogenous mechanisms, resulting in its perseveration. Echopraxia can arise in the context of basal ganglia dysfunction, as well as after frontal lobe damage. It is probable, however, that in both cases the mechanism that underlies echopraxia is a disinhibition of the mirror areas through loss of suppression by the frontal lobe. ³²
1.5.4 Motor–sensory mismatch

Recent clinical and experimental work indicates that the central nervous system may be critical in generating a feedback-dependent state, which can produce pathological sensations in some patients independent of any initial peripheral pathology.

It is indicated that central nervous systems that generate motor activity are closely coupled to sensory feedback systems and are monitored to detect deviations from that predicted. Increased neuronal activity has been detected within the central nervous system, specifically in the right dorsolateral prefrontal cortex (RDPC: this region is active during complex motor tasks and those that require increased motor effort), when incongruent information has been received from the periphery suggestive of a mismatch between intention, proprioception and visual feedback.

In 2005 Dr. Candida McCabe carried out a study with the purpose to discover whether pain could be induced in pain-free healthy volunteers, when a conflict between motor–sensory central nervous processing was generated transiently in a laboratory setting. The outcome of the study is that a difference between motor feedback and the predicted somatosensory feedback can produce anomalous sensory symptoms, such as:

- Discomfort to mild pain
- Temperature change
- Weight change
- Perceived loss of or additional limbs
- Feelings of peculiarity

The primary cause of mediated changes between the motor and predicted somatosensory feedback may lie within the motor control system, whose role is to manage the relationship between motor commands and sensory feedback.

Motor control system

In order to be effective, the motor control system has to maintain a broad overview of the body’s current state via the ‘state variables’ (e.g. joint position sense, body schema), but also work at the lower local level, to know exactly which muscles are required to deliver a specific movement. The higher and lower levels must interact in order to deliver the optimum method, i.e. the most efficient method. Smoothness of movement has been proposed as an ultimate aim of the motor control system, best achieved by unifying limb and eye movements.

Mechanism of motor-sensory mismatch

The environment, the musculoskeletal system and sensory receptors all influence the transformation of motor commands to their sensory consequences. These sensations in turn influence the subsequent motor commands. Therefore, a feed-forward and feedback system is constantly in action, and it is at the interaction between the two (where actual sensory input meets the predicted sensory input), that sensory disturbances may be generated.
The larger the motor command required (when smooth movement becomes more difficult to achieve) the greater the sensory abnormalities. In mild sensory changes, an early warning system is alerting the individual to abnormalities within information processing. If these sensory changes persist and the threat is perceived as greater, then ultimately pain will be produced.

These monitoring mechanisms can be triggered by externally produced conflict (e.g. incongruent movement whilst viewing the mirror) or internally (e.g. the ageing process leading to inaccurate execution of movement and/or altered proprioception, or disease damage in rheumatoid arthritis resulting in stiffness).

The concept that a motor–sensory mismatch gives rise to anomalous sensations including pain is new and thus far has found most of its evidence from the study of patients with chronic pain. Many normal subjects (without clinical pathology) can experience a wide range of sensory disturbances, including localized pain, when exposed to transient motor–sensory conflict.

Examples of motor-sensory mismatches
Conditions that occur in the absence of a identifiable peripheral causal pathology or appear disproportionate to the size of the injury are:

- Repetitive strain injury
- Complex regional pain syndrome-type 1 (CRPS)
- Fibromyalgia
- Focal hand dystonia
- Phantom limb pain
1.6 Conclusions

The mirror neuron system helps individuals to learn from each other, to associate sounds and intentions with actions. Mirror neurons fire if the individual is performing actions.

Being touched and seeing someone else touched activates the same neural circuits. There is activity in the Secondary somatosensory cortex (SII). Mirror neurons also occur in SII. If the motor and sensory feedback is the same, the motor-sensory mismatch doesn’t arise. But what if mirror neurons do not work correctly? Then what you feel isn’t the same as what you see.

A logical step to integrate mirror neurons in the aspects of chronic pain, would be to look at specific symptoms of patients with chronic pain. Patients with chronic pain:

- Have reduced proprioceptive acuity
- Have a cortical representation of the relevant body part that is markedly different to healthy people
- Find subtle movements more difficult than people without chronic pain do

A mismatch between motor output and sensory input triggers a warning mechanism based within the motor control system, which generates a dissensory state. In this state, the individual may experience a range of sensory disturbances, including pain. The altered proprioception shown above and difficulties in subtle movements can result in a motor-sensory mismatch, which in its turn causes pain or other sensory abnormalities. This integration is just a speculation that requires more research.

Mirror neurons can be seen as body maps that run simulations of what other peoples body maps are up to. They help us in understanding and possibly feeling the emotions of others by simulating their facial expressions. Hereby it is linked with empathy and emotions.
Chapter 2.
Body maps, plasticity, emotions and their connection with pain
2.1 Introduction

The body and brain are engaged in a continuous interaction that unfolds in time, within different regions of the body and within mental space as well.

1. Mental states (like emotions) cause brain states
2. Brain states cause body states
3. Body states are then mapped in the brain and incorporated into the ongoing mental states.

A small change on the brain side of the system can have major consequences for the body state. But a small change on the body side (think of a knife cut) can have a major effect on the mind once the change is mapped as a nociceptive state and perceived as acute pain.

Networks that link the mind and the body are:
- The ‘body-loop’: the information-processing network of the brain, that takes care of faithful and current information of the various physiological parameters at different regions of the body.
- The ‘as-if-body-loop’: the simulation, in the brain’s body maps, of a body state that is not actually taking place in the organism.

2.1.1 Connection with Mirror Neurons

The mirror-neuron system achieves what is hypothesized as the ‘as-if body loop’ system. The fact that the body state that the mirror neurons are simulating is not the subject’s, means that if a complex brain can simulate someone else’s body state, it can simulate one of its own body states.

This simulation of own body states can be developed for a clear and immediate advantage:
Rapid and energy-saving activation of the maps of certain body states, which were, in turn, associated with relevant past knowledge and cognitive strategies.

2.1.2 Emotions and brain mapping

In certain circumstances, as an emotion unfolds, the brain rapidly constructs maps of the body comparable to those that would result were the body actually changed by that emotion.

- The brain can simulate a certain body state as if it were occurring, and because perception of any body state is rooted in the body maps of the somatosensing regions, the body state is perceived as actually occurring even if it is not.
- The brain structures in charge of triggering a particular emotion. The brain is also able to connect brain areas in which the body state corresponding to the emotion would be mapped.

In this Chapter the body maps of the somatosensing regions and its disorders are explained. The somatosensory cortex also has cross links with parts of the brain that are involved with emotions. In this chapter the link between body maps, emotions and pain is described.
2.2 Body maps

Wilder Penfield, a surgeon of the Montreal Neurological Institute, made a complete brain map of the body surface in his study in 1940. He probed in patients brain with electrodes and found different spots according to different parts of the body. In 1950 he made a complete brain map, and named it the Homunculus (literally 'little man'). He found the sensory homunculi and the motor homunculi. He wrote a book called 'The cerebral cortex of man' and hired an illustrator to draw pictures of the found homunculus (Figure 1). This quickly became iconic of neuroscience.

The homunculus has ridiculous proportions, these proportions depend on the amount of receptors or coordinated muscle groups found in body parts.  

Figure 1 W. Penfield and T. Rasmussen 1950

Aspects of the outside world and the bodies anatomy are systematically mapped onto brain tissue. This is called a body map. There are three kinds of body maps: the primary motor body map, the primary visceral body map and the primary sensory body map.

2.2.1 Primary motor body map

The primary motor map makes movements. Instead of receiving inputs from your skin, this map sends output signals to your muscles. It’s vital to your ability to guide your body parts to make fine-tuned movements and assume complex positions in space. Thanks to this map, all the low-level, mostly unconscious tasks of coordinated movement unfold smoothly without a glitch.
2.2.2 Primary visceral body map
The primary visceral map is a patchwork of small neural swatches that represent your heart, lungs, liver, colon, rectum, stomach, and all your various other giblets. This map is located elsewhere in your brain.

2.2.3 Primary sensory body map
The topology of the body's surface is preserved in the sensory body map or touch map. This map is the primary physical window to the world around a person. The entry point for all touch information is streaming moment by moment into the brain. Once the sensory information reach your brain they are combined to create complex, composite sensations. In the sensory map different receptive areas of the skin and organs are presented next to each other.

Somatic senses are:

- Touch (pressure: gentle, deep, vibration)
- thermoception (warm, cold, too warm/cold becomes nociception)
- Nociception (injury after trauma, piercing, heat, chemical, joint, deep, tickle, itch)
- Proprioception (body's position and motion in space)
- Balance (in the inner ear, unchanged in design for half a billion years)

The somatic sensory system is the most diverse of the sensory systems, mediating a range of sensations. These sensations are transduced by receptors within the skin of muscles and conveyed to a variety of central nervous system targets. This complex neurobiological machinery can be divided into functionally distinct subsystems with distinct sets of peripheral receptors and central pathways.

1. One subway transmits information from cutaneous mechanoreceptors and mediates the sensation of fine touch, vibration, and pressure.
2. Another originates in specialized receptors that are associated with muscles, tendons, and joints and is responsible for proprioception (sense the position of the limbs and other body parts in space)
3. The third subsystem arises from receptors that supply information about painful stimuli and changes in temperature as well as coarse touch.

This paragraph focuses on the somatic sensory cortices and the mechanisms responsible for sensations of pain, temperature and coarse touch.

Primary somatic sensory cortex
The primary somatic sensory cortex in humans (also called SI) is located in the postcentral gyrus of the parietal lobe and comprises four distinct regions, or fields, known as:

1. Brodmann’s area 3a
2. Brodmann’s area 3b
3. Brodmann’s area 1
4. Brodmann’s area 2 (see Figure 2)
Figure 2

A salient feature of somatotopic maps is their failure to represent the human body in its actual proportions. In the representation of the human body in the primary sensory (and motor) cortex, the homunculus had grossly enlarged face and hands compared to the torso and proximal limbs. These anomalies arise because manipulation, facial expression, and speech are extremely important for humans and require a great deal of circuitry, both central and peripheral, to govern them. To accommodate the extra circuitry, the density of receptors is greater in regions such as the hands and lips.

Functions

Functional properties of the neurons in each region are distinct. Experiments carried out in non-human primates indicate that:

- Neurons in areas 3b and 1 respond primarily to cutaneous stimuli
- Neurons in area 3a respond mainly to stimulation of proprioceptors
- Neurons in area 2 respond to both tactile and proprioceptive stimuli

Area 3b receives the bulk of the input from the ventral posterior complex and provides a particularly dense projection to areas 1 and 2. This arrangement of connections establishes a functional hierarchy in which area 3b serves as an obligatory first step in cortical processing of somatosensory information (see Figure 3).
2.2.4 Beyond the primary somatic sensory cortex

Somatic sensory information is distributed from the primary somatic sensory cortex to ‘higher order’ cortical fields. One of these higher order cortical centers, the secondary somatosensory cortex (SII) lies in the upper bank of the lateral sulcus. SII receives convergent projections from all subdivisions of SI, these inputs are necessary for the function of SII. Lesions of SI eliminate the somatosensory responses of SII neurons. Area SII sends projections in turn to limbic structures such as:

- The amygdala
- The hippocampus (see Figure 3)

This latter pathway is believed to play an important role in tactile learning and memory.

Neurons in SI also project to parietal areas posterior to area 2, especially areas 5a and 7b. these areas receive direct projections from area 2 and, in turn, supply inputs to neurons in motor and premotor areas of the frontal lobe. This is a major route by which information derived from proprioceptive afferents signalling the current state of muscle contraction gains access to circuits that innate voluntary movements.

The projections from parietal cortex to motor cortex are critical for the integration of sensory and motor information. 43

2.2.5 Experience of pain

The presentation of a painful stimulus results in the activation of both primary somatosensory cortex and anterior cingulated cortex.

- Changes in intensity are highly accompanied by changes in the activity of neurons in the somatosensory cortex
- Changes in unpleasantness are highly correlated with changes in the activity of neurons in the cingulated cortex

From this description, it should be evident that the full experience of pain involves the cooperative action of an extensive network of brain regions whose properties are only beginning to be understood. 44

There are two pathways for transmission of somatosensory information to the central nervous system: the dorsal column system and the anterolateral system of the spinal cord. The dorsal column system processes the sensations of fine touch, pressure, two-point discrimination, vibration, and proprioception (limb position). The anterolateral system processes the sensations of pain, temperature, and light. 45

Specific fibers in the anterolateral system project to a number of different structures in the brainstem and forebrain, making it clear that pain is processed by a diverse and distributed network of neurons. These central destinations are likely to mediate different aspects of the sensory and behavioral response to a painful stimulus.

1. One component of this system mediates the sensory-discriminative aspects of pain:
   a. Location
   b. Intensity
   c. Quality of the noxious stimulation
These aspects of pain are through to depend on information that is relayed through the ventral posterior lateral nucleus (VPL) to neurons in the primary and secondary somatosensory cortex.

2. Other parts of the system convey information about the **affective-motivational** aspects of pain:
   a. Unpleasant feeling
   b. Fear
   c. Anxiety
   d. Autonomic activation that accompany exposure to a noxious stimulus

Targets of these projections include several subdivisions of the reticular formation, the deep layers of the superior colliculus, the central grey, the hypothalamus, and the amygdala. A distinct set of thalamus nuclei (midline thalamus nuclei) are thought to play an important role in transmitting nociceptive signals to the anterior cingulated cortex, and to the insula (see Figure 4).

**Figure 4**

![Diagram of pain theories](image)
2.3 Plasticity and Remapping

2.3.1 Plasticity

Brain maps chart not only your body, but also the space around your body. These maps expand and contract to include everyday objects. These maps can even be shaped by the culture you grow up in. Research now shows that the brain has:

- Maps of your body's surface
- Maps of your body's musculature
- Maps of your body's intentions
- Maps of your body's potential for action
- A map that automatically tracks and emulates the actions and intentions of other people around you (see Chapter 1. Mirror Neuron System)

These body centered maps are profoundly plastic thus are capable of significant reorganisation in response to:

- Damage
- Experience
- Practice

Formed early in life, body maps mature with experience and then continue to change for the rest of your life. The body maps parameters are constantly changing and adapting, every minute. The constant activity of your body maps is so seamless, automatic, fluid and ingrained, that it is not even recognized that it’s happening. 47

Any time someone is learning something new, any time the brain deems an experience worthy of remembering over the long term, new connections sprout between cells and previously existing connections are strengthened. This process is called plasticity. 48

Hebbian learning

Hebbian learning is a group of biologically inspired unsupervised learning algorithms. They are based around the idea that a connection is strengthened by it repeatedly being activated. The theory is often summarized in simple form as "cells that fire together, wire together".

Hebb's rule, also called cell assembly theory, was introduced by Donald Hebb in 1949 and states:

Let us assume that the persistence or repetition of a reverberatory activity (or "trace") tends to induce lasting cellular changes that add to its stability.... When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased. 49

If pain is experienced, different neurons can be connected to a so-called pain network in the brain. The neurons involved in this network fire and wire together even if they normally have nothing to do with each other. The pain network is more sensitive for a
combination of weak stimuli or for strong stimuli that are similar to the weak stimuli (Figure 5).

Figure 5.  

![Hypothetical Neural Circuit](image)

Functional
Plasticity can be functional in new practices and experiences, or in loss of digits because of the new connections that are made in the brain. After brain damage (for example a stroke) patients learn to compensate the function loss via plasticity. In some cases the opposite hemisphere takes over part of the functions.

Functional remapping also occurs in the somatic sensory nuclei in the thalamus and brainstem. Similar plastic changes have been demonstrated in the visual, auditory, and motor cortices, suggesting that some ability to reorganize after peripheral deprivation of injury is a general property of the mature neocortex. 51

2.3.2 Remapping disorders
Plasticity is not always functional, it can cause different disorders. In this paragraph two remapping disorders are discussed.

Phantom limb pain
Almost everyone who has a limb amputated will experience a phantom limb, the vivid impression that the limb is not only still present, but in some cases, painful. There is now a wealth of empirical evidence demonstrating changes in cortical topography in primates following deafferentation or amputation, and this review will attempt to relate these in a systematic way to the clinical phenomenology of phantom limbs. 52

It is know that a complete somatotopic map of the body’s surface exists in the somatosensory cortex of primates including humans. Ramachandran and others show that if you loose a limb, your brain begins to remap your body within hours.

A phantom is born as plasticity reorganizes touch maps and motor maps in the Penfield homunculi. Sometimes phantoms go away, presumably because the brain learns to predict and accept sensations from the newly fused brain maps. Some phantoms persist for decades. Phantoms can produce several sensations such as:

- Pain
- Burning
• Tingling
• Paralyzed feeling

Some patients experience the feeling of being able to move their phantoms. This can be explained by the intact motor maps that send out normal commands. 53

**Remapping hypothesis**

One rule of organisation of the cortical topography is that each peripheral neuron gets an equal cortical area/homunculus. After amputation the cortical zone of the amputated body part does not die of go numb after sensory loss. Fibers from an adjacent body map will invade in that cortical area. Plasticity sets in right away. 54 55

An example of invaded fibers in cortical areas is the study of V.S. Ramachandran et al in the year 1998. They concluded that following amputation, the somatotopic representation of the phantom limb can be activated by stimulation of other body areas. The somatosensory cortex of primates has complete maps of the entire body surface. Following partial denervation, the representation of an adjacent body part may ‘expand’ over time into the deafferented area. For example, weeks after deafferentation of the hand, there is striking remapping of the face on to the hand region of the map in somatosensory cortex I (3b) (Figure 6).

**Figure 6.**

![Figure 6](image)

Somatotopic representation of phantom sensations in the hand following activation of the face with different stimuli 24 h after amputation.

In the study of Peter Söros et al, is also shown that acute pain causes rapid functional reorganization of the somatosensory cortex. Future research is necessary to define the importance of somatosensory plasticity for the chronification of pain. 57
Dystonia
The highly flexible, dynamic process of plasticity can go awry. There is such a thing as overlearning, as in too much plasticity. If a movement is repeated too often and someone suffers from biological vulnerabilities, this can result in frozen, fused, malformed or disturbed body maps. Motor programs become tangled together, receptive field enlarge and cortical maps overlap each other. These disturbances and tangles can result in random muscle contractions that can result in painful and pointless movements. Such conditions are known as dystonias, a group of body map disorders involving abnormal muscle tone and control. Dystonias can differ case by case. 58
The cortical map abnormalities relate to the types and magnitudes of dysfunction. For example: because of the overlearning, tasks can not be performed individually. 59

Focal hand dystonia
In the year 2002 Nancy Byl performed different studies in focal hand dystonia. These studies showed that animals, including humans, commonly compensate for difficulties in motor control by applying more repetition, attention, and stereotypy to the task performance. At some point the reduction of independence of available sensory feedback causes conflict between different motor programs, and the result is a pathologic movement dysfunction called focal hand dystonia.

The hand representation is located in primary somatosensory cortex, Area 3b. Area 3b is necessary for hand functionality in fine discriminative tasks. Pathways from Area 3b may be responsible for carrying the abnormal sensory feedback cues in dystonia. The exact pathway by which this abnormal feedback occurs is not known.

The study concluded that:
- Receptive fields were up to ten times larger than normal (plasticity to receptive field enlargement in a sensory–motor task)
- Abnormal combinations of receptive fields and large sectors of the somatosensory thalamus with continuous representations were also found in human general dystonia patients
- Abnormally large receptive fields were found ipsilateral to the focal hand dystonia, in the representation of the other untrained hand. Receptive field overlap was also abnormal ipsilaterally to the dystonia. The ipsilateral physiological abnormalities indicate that some mechanism not specific to the sensory input contributes to the disorder. 60

In other words most dystonias seem to be rooted in one kind or another of body map dysfunction. The exact substrate for this disorder is not known.
2.4 Emotions

The Somatosensory cortex incorporates signals arising in the musculoskeletal system and the vestibular system. These cortices are richly interconnected with those of the insula. The insular cortex is largely concerned with visceral and autonomic function, including taste. Signals from the body's interior ultimately come together in the insula (see Figure 7). 61

The cross signaling between the somatosensory cortex and the insula provides a composite and continuous map of the body state that brings together the internal milieu and viscera along with the invariant aspects of the musculoskeletal system.

The same parts of the insula (the right frontal insula) are involved systematically in the feelings of emotion along with other regions of the central nervous system in the brainstem and diencephalon. Emotions such as:

- Happiness
- Anger
- Fear
- Sadness 63
2.4.1 Emotions

An emotion, be it happiness or sadness, embarrassment or pride, is a patterned collection of chemical and neural responses that is produced by the brain when it detects the presence of an emotionally competent stimulus, an object or situation, for example. Emotions are the most visible part of a huge biological regulation that includes the homeostatic reactions that maintain metabolism, pain signalling, and drives such as hunger and thirst.

Reaction of the brain

Emotional responses are a mode of reactions of the brain that are prepared by evolution to respond to certain classes of objects and events with certain repertoires of action. Eventually, the brain associates other objects and events that occur in individual experience with those that are innately set to cause emotions, so that another set of emotionally competent stimuli arises.

Reaction of the body

The main target of the emotional responses is the body:
- The internal milieu
- The viscera
- The musculoskeletal system

But there are also targets within the brain itself, for example specific nuclei in the brainstem.

The result of the body-targeting responses is the creation of an emotional state, involving:
- Adjustments in homeostatic balance
- The playing of specific behaviors (such as freezing or fight-or-flight, and the production of particular facial expressions)

This brain-targeting responses result in an alteration in the mode of brain performance during the emotional body adjustments. The consequence is, for example, a change in the attention accorded to stimuli.

Emotions are not subjective, private or undefinable. Their neurobiology can be investigated objectively, not just in humans but in laboratory species.

2.4.2 Feelings

- Feelings are the mental representation of the physiological changes that characterize emotions. Unlike emotions, which are scientifically public, feelings are private, although no more subjective than any other aspect of the mind.
- Feelings are the direct consequences of emotions, the clarification of emotional neurobiology opens the way to explain the neurobiology of feelings. 64
2.5 Pain is a homeostatic emotion

The basic homeostatic ‘feelings’, or modalities, include:
- Temperature
- Itch
- Visceral distension
- Muscle ache
- Hunger
- Thirst
- ‘Air hunger’
- Sensual touch

Pain normally originates from a physiological condition in the body that automatic (subconscious) homeostatic systems alone cannot rectify, and it comprises a sensation and a behavioral drive with reflexive autonomic adjustments. Pain can be either unpleasant (as usual) or pleasant (as when it relieves an intense itch).

The behavioral drive that is called pain usually matches the intensity of the sensory input but it can vary under different conditions, and can become intolerable or, alternatively, disappear, just as hunger or thirst.

Interactions of pain with homeostatic conditions and with emotional status unifies the different conditions that can cause different types of pain from different tissues under a common homeostatic function, in maintenance of the balance of the body.

Emotions consist of a sensation and a motivation with direct autonomic effects. Pain is one of many distinct homeostatic emotions that directly reflect the condition of the body.

Pain in humans is a homeostatic emotion reflecting an adverse condition in the body that requires a behavioral response. It involves:
- A distinct sensation, engendered in interoceptive and anterior insular cortex \(\rightarrow\) the feeling itself
- And an affective motivation, engendered in the ACC (anterior cingulated cortex) \(\rightarrow\) the behavioral agent

2.5.1 Pain interacts with homeostatic functions

The discriminative, topographic representations in interoceptive cortex obviate the involvement of SI in feelings from the body. Viewing pain as a homeostatic emotion readily incorporates the interactions of pain with other homeostatic functions and with emotional state, such as in psychosomatic illness.

It remains to be seen how endogenous homeostatic control mechanisms provide integrated modulation of the afferent activity that produces the emotion of pain, and how these might best be engaged by clinical intervention.65
2.5.2 Involved brain areas

The neural systems that are involved in the production of emotions are being identified through studies of humans and other animals. Various structures trigger emotions by functioning as interfaces between the processing of emotionally competent stimuli and the execution of emotions, such as:

1. Amygdala
2. Ventromedial prefrontal cortices

But the real executors of emotions are:

3. Structures in the hypothalamus
4. Structures in the basal forebrain (the nucleus accumbens)
5. Structures in the brainstem (the nuclei in the periaqueductal grey)

These are the structures that directly signal, chemically and neurally, to the body and brain targets at which alterations constitute an emotional state.

Functional imaging studies also reveal that body-sensing areas show a statistically significant pattern of activation or deactivation when normal individuals experience the emotions of sadness, happiness, fear and anger. Areas such as:

6. Cortices in the insula
7. Second somatosensory region (SII)
8. Cingulate region of the brain (ACC)

Those body related patterns are tangible neural correlates of feelings and emotions. 66
2.6 Conclusions

The as-if body loop (mirror neurons) and the body loop (body maps) all point to functions of the perception of the body during the experience of an emotion: The emotion ends up felt in the body.

Feelings of emotion are just as mental as any other perception, but a sizable part of the objects being mapped are states of the living organism in which the feelings arise. In the feeling of emotion, the object itself: the **body**, can be changed radically.

For a period of seconds or even minutes after a feeling begins, a dynamic engagement of the body leads to a dynamic variation of the perception. Part of the variation may even be due to the changes in **homeostatic** necessity caused by the emotive process.

The body and brain inhabit the same organism, and the relationship between the two can be entirely circular. 67

Viewing pain as a homeostatic emotion readily incorporates the interactions of pain with other homeostatic functions and with emotional state, such as in psychosomatic illness.

A lot of the brain areas that are involved in emotional states, are also involved in pain perception (see Table 1). This could mean that emotions and pain can’t be dissociated from each other.

### Table 1

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Emotions</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ventromedial prefrontal cortices</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Insula</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Somatosensory cortices</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cingulate cortex (ACC)</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Chapter 3.
Innate immune system, cytokines, sickness behavior and emotions
3.1 Introduction

Almost any neuroscience or neurology textbook will describe how noxious stimuli (stimuli that damage or threaten to damage tissues of the body) activate a system that begins with the peripheral terminals of primary sensory neurons, continues with relays through spinal and supraspinal nuclei, and leads to the activation of a matrix of cortical areas that is associated with the multiple conscious dimensions of pain. Knowledge of this system dates back several hundred years, and is now considerable. Many of the attempts to provide relief to those in pain have sought to surgically or pharmacologically target this neuronal system at one level or another, mostly with only limited success. One reason for this failure is that the model is incomplete.

- Not only does it make no allowance for the context in which pain is usually perceived and the modifying influences of emotions like fear and anxiety or anticipation and pain history (discussed in Chapter 2).
- But it is also neurobiologically incomplete. Some important features of neuronal processing have been overlooked or ignored in the traditional depiction of the model.

The recent idea is that cells of the immune system might strongly influence neuronal function in many persistent or chronic pain states. New research indicates that immune cells have an important role as pain modulators not just in inflamed tissues, but also in damaged peripheral nerves and in the central nervous system.

In this Chapter the role of the immune system is discussed, the innate immune system in particular. During the activation of the innate immune system cytokines are released, cytokines are proteins that make you feel sick. Signals of cytokines can enter the brain through several pathways. Once in the brain these signals result in sickness behavior. Sickness behavior can be maintained, and can therefore cause different behavioral changes, like depression.
3.2 Immune system

The immune system is a complex network of specialized cells and organs (lymphoid organs) that distinguish between self and non-self, and defends the body against infections caused by agents such as bacteria, viruses, fungi and parasites.

To protect against potentially pathogenic micro-organisms that are foreign to the body (antigens), the host uses white blood cells, or leukocytes, that all originate from precursors in the bone marrow. These cells circulate through the blood and lymph system or are fixed in specific tissue. To establish an infection, the pathogen must first overcome numerous surface barriers, such as enzymes and mucus. Any organism that breaks through this first barrier encounters the two further levels of defense, the innate and adaptive immune responses.

Immunity is divided into two parts determined by the speed and specificity of the reaction. These are named the innate and the adaptive responses, although in practice there is much interaction between them.

1. The term innate immunity is sometimes used to include physical, chemical, and microbiological barriers, but more usually encompasses the elements of the immune system (neutrophils, monocytes, macrophages, complement, cytokines, and acute phase proteins) which provide immediate host defence. The innate response is rapid but sometimes damages normal tissues through lack of specificity.

2. Adaptive (acquired) immunity is the hallmark of the immune system of higher animals. This response consists of antigen-specific reactions through T lymphocytes and B lymphocytes. The adaptive response is precise, but takes several days or weeks to develop. The adaptive response has memory, so that subsequent exposure leads to a more vigorous and rapid response, but this is not immediate.

More characteristics of the two immune responses are shown in Table 1.

<table>
<thead>
<tr>
<th>Physical and chemical barriers</th>
<th>Innate Immune Response</th>
<th>Acquired Immune Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin, mucous membranes</td>
<td>Phagocytes (macrophages, neutrophils, natural killer cells)</td>
<td>Lymphocytes (B and T cells)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Soluble mediators</th>
<th>Innate Immune Response</th>
<th>Acquired Immune Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage-derived cytokines, e.g., IL-1, IL-6, TNF-α, IFN-γ</td>
<td></td>
<td>Lymphocyte-derived cytokines, e.g., IL-2, IL-4, IL-5, IL-6, IL-10, IFN-γ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recognition specificity</th>
<th>Innate Immune Response</th>
<th>Acquired Immune Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toll-like receptors</td>
<td>Recognition of crude molecular patterns (e.g.,</td>
<td>Recognition of specific microbial and nonmicrobial antigens (e.g., T-cell receptor)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Memory</th>
<th>Innate Immune Response</th>
<th>Acquired Immune Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Circulating effector molecules</th>
<th>Innate Immune Response</th>
<th>Acquired Immune Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement, acute phase reactants</td>
<td></td>
<td>Antibodies</td>
</tr>
</tbody>
</table>

The innate immune system can contribute to the onset and preservation of different disorders. The next paragraph will clarify this.
3.2.1 Innate immunity

Innate immunity represents the first line of defence against antigens and involves phagocytic cells that are mononuclear (macrophages) and polymorphonuclear (neutrophils). These cells capture microbes and digest them, and the mononuclear macrophages also present antigen fragments to lymphocytes. Lymphocytes recognize antigens and release interferons (IFNs) in response to the presence of pathogens. Interferon alpha (IFN-alpha) then activates the inflammatory cytokine network and is associated with a high rate of behavioral changes. These cytokines then orchestrate the local immune response by recruiting and activating relevant immune cells, which leads to the swelling (tumor), redness (rubor), heat (calor), and pain (dolor) that constitute the clinical characteristics of inflammation.

Cells of the innate immune response

- Phagocytic cells (neutrophils, monocytes, and macrophages) White blood cells of the innate immune system. They engulf a particle or pathogen.
- Cells that release inflammatory mediators (basophils, mast cells, and eosinophils)
- Natural killer cells. They destroy compromised host cells (tumors/virus-infected cells)

Innate responses frequently involve complement, acute-phase proteins, and cytokines. Cytokines constitute a group of soluble mediators. They act as messengers both within the immune system and between the immune system and other systems of the body, forming an integrated network that is highly involved in the regulation of immune responses.

3.2.2 Cytokines

Cytokines are protein molecules whose name derives from early observations that these molecules influenced cell (‘cyto’) movement (‘kinesis’). Within the cytokine network, some cytokines act to promote inflammation whereas other ones, known as anti-inflammatory cytokines, oppose this response by attenuating the production of proinflammatory cytokines or by opposing their action at the receptor level.

- Pro-inflammatory cytokines are for example:
  - Interleukin (IL)-1
  - Interleukin (IL)-6
  - Tumor necrosis factor (TNF)-alpha
- Anti-inflammatory cytokines are for example:
  - IL-10

3.2.3 Pathways of immune to brain signalling

Proinflammatory cytokines are produced by cells of the innate immune system in response to pathogen-associated molecular patterns and to endogenous danger signals.
act on the central nervous system via **afferent** and **humoral** pathways to trigger a brain cytokine system that organizes the sickness response in its subjective, behavioral, and metabolic components. 79

Cytokines act on the brain via two communication pathways:

1. A neural route represented by the primary afferent neurons that innervate the body site where the infection takes place (fast pathway)
2. A humoral pathway that involves the production of IL-1 by phagocytic cells in the circumventricular organs (CVOs) and choroid plexus, followed by its diffusion to brain target areas and its possible relay by prostaglandin intermediates (slow pathway) 80

Figure 1

Proinflammatory cytokines produced by activated innate immune cells induce sickness behavior by a centrally mediated action in addition to their role in the mounting of the peripheral immune response.

Peripheral immune response

A peripheral pathogen results in activation of inflammatory cells. This is classically associated with pain (dolor), heat (calor), redness (rubor), swelling (tumour) and loss of function. However, new research indicates that immune cells have an important role as pain modulators not just in inflamed tissues, but also in damaged peripheral nerves and in the CNS. 81

Cytokines are relatively large molecules and, therefore, do not freely cross the blood–brain barrier (BBB) under usual circumstances (in the absence of infection). Peripherally released cytokines act on the brain via a fast transmission pathway involving primary afferent nerves innervating the bodily site of inflammation and a slow transmission pathway involving cytokines originating from the choroid plexus and circumventricular organs and diffusing into the brain by volume transmission. (Figure 2) 82

Figure 2. 83
Vagus Nerve

- The vagus nerve is likely to be both directly and indirectly activated by proinflammatory cytokines. \(^{84}\)
- The vagus nerves that innervate organs of the abdominal cavity, contain macrophages and dendritic cells that produce IL-1. Sensory neurones of the vagus nerves express receptors for IL-1, and IL-1 stimulates vagal sensory activity.
- Vagal afferents have been shown to mediate at least partially the induction of sickness behavior, as well as the neural activation of the brainstem, hypothalamus and limbic structures in response to peripherally administered LPS (lipopolysaccharide) and IL-1.

The role of vagal afferents is less important for fever than it is for the behavioral depression that develops in response to peripheral immune stimuli. This indicates that the mechanisms of communication between the periphery and the brain are not the same for these different components of the inflammatory response.

Brain response

Once cytokine signals reach the brain, these signals can be transmitted and amplified within the context of the cytokine network in the brain. Receptors for proinflammatory cytokines are located in the brain, including brain regions that play important roles in emotional regulation, neurovegetative function and cognition:

- hypothalamus
- hippocampus \(^{85}\)

If proinflammatory cytokines signals enter the brain, this results in sickness behavior. \(^{86}\)

3.2.4 Sickness behavior

The behavior of sick people changes dramatically, they often feel feverish and nauseated, ignore food and beverages, and lose interest in their physical and social environments. They tire easily and their sleep is often fragmented. In addition, they feel depressed and irritable, and can experience mild cognitive disorders ranging from impaired attention to difficulties in remembering recent events. \(^{87}\)

The psychological and behavioral components of sickness represent, together with the fever response and the associated neuro-endocrine changes, a highly organized strategy of the organism to fight infection. This strategy, referred to as ‘sickness behavior’ is triggered by the pro-inflammatory cytokines.

Sickness behavior exhibits many overlapping features with mood and anxiety disorders, including:

- Depressed mood
- Irritability
- Anger/hostility
- Fatigue
- Anorexia
- Psychomotor slowing
• Altered sleep patterns
• Anhedonia
• Impaired memory and concentration

The development and duration of sickness behavior is regulated by anti-inflammatory cytokines.

3.2.5 Motivation

Cytokines function as a motivational signal that tells the brain to change the organism priorities. In face of the threat represented by pathogen or danger signals a reorganization process sets in. Behavioral changes that are observed are those that can be predicted by the motivational hypothesis, rather than by the energy supply model. This means motivation is more important than physical state. Because of this fact sickness behavior can be maintained by emotional/motivational states.
3.3 Immune system and behavioral changes

Sickness becomes abnormal/pathological when:
- Intensity is disproportionate in relation to it’s eliciting factors
- It occurs in the absence of any immune triggering stimulus

Normally, the production and action of proinflammatory cytokines are tightly regulated by a wide variety of opposing molecular factors including anti-inflammatory cytokines, glucocorticoids, and neuropeptides (Figure 3). These factors are operational both at the periphery and in the brain. In case of glucocorticoid resistance or during chronic inflammation, this opposing system can become inefficient and prolonged activation of the cytokine system ensues. This can result in mood disorders.

Figure 3.  

Regulation of the expression and action of peripheral and brain cytokines by anti-inflammatory cytokines, glucocorticoids and neuropeptides such as vasopressin (AVP). Peripheral cytokines are produced by innate immune cells that are normally activated by pathogen-associated molecular patterns (PAMPs) but they can also be activated by endogenous danger signals including oxidative stress.

A sensitized brain cytokine system is less likely to turn off when the danger is over and more likely to be triggered by extrinsic non-immune stimuli, like emotions and stress.

In the next paragraphs different non immune stimuli that can cause prolonged activation of the cytokine system are discussed.
3.4 Non Immune stimuli

3.4.1 Ageing
Ageing is associated with increased activity of the innate immune system, which at the brain level translates into an enhanced production of pro-inflammatory cytokines, such as IL6, and a decreased production of anti-inflammatory cytokines, including IL10.

- Chronic inflammatory mechanisms carry the imprint of early-life infections into later life morbidity and mortality.
- Inflammatory responses can be induced by invading pathogens, as well as by trauma or internal tissue injury. Thus, adaptive responses to short term infections or injury can become maladaptive as life progresses.
- The immune response also depends on the genetic background of individuals.

With ageing, the reason why the innate immune system becomes over-activated is not clear, but increased exposure to infectious agents or cumulative damage to tissues could spark the change.\(^92\)

3.4.2 Emotional states
Bodily states may play a pivotal role in the regulation of mental processes including emotion. Signals emanating from the body's activated immune system (cytokines) access the brain and alter brain function. These immunologic influences on the brain include the induction of emotional states such as depression, anxiety and irritability.

Activation

- Contributions of bodily processes to emotion regulation are especially relevant in individuals suffering from a variety of medical illnesses, where the rate of emotional distress is high, and immune activation and inflammation with the resultant release of inflammatory cytokines, is common.
- Chronic stress also activates the immune system.

Bodily states, in particular those involving activation of innate immune responses, are associated with emotional dysregulation.

There are multiple potential pathways by which cytokines can influence emotional state. The role of the body, in general, and the immune system, in particular, in behavioral regulation come from recent findings that psychological stressors have the capacity to activate early, innate immune responses and their signaling pathways in humans.

The behavioral consequences of stress, including emotional dysregulation, may in part be mediated by the influence of the immune system on the brain.\(^93\)

Somatization

Somatization is the tendency to express emotional problems in somatoform symptoms. It is nothing else than sensitization of the brain cytokine system.\(^94\)
3.4.3 Stress

Stress response
The stress response is a conserved, physiological coping reaction to adverse environmental conditions, as diverse as physical and/or psychological constraints, injuries, trauma, poor microclimate and others.

A cytokine response in the brain can be mounted in different forms and extent by the host after exposure to both infectious and non-infectious stimuli. The brain produces interferon-a (IFN-a) in response to non-inflammatory as well as inflammatory stress. 95

The neuroendocrine system spreads hormones from the hypothalamus. These hormones regulate the function of specific organs. The interaction between the immune and the neuroendocrine systems is bidirectional. Pathways do not serve only to transmit information from the brain to visceral organs. They also feed sensory information from the visceral organs to the brain.

Behavior
Behavioral responses to stress can be either active, when an organism attempts to control the situation, or passive, when the organism cannot control the situation and withdraws from it. This mechanism is controlled in the brain by two opposite systems:
1. a behavioral activation system
2. a behavioral inhibition system
The concept that has emerges in stress research is that the inability to control the situation actively leads to a high state of arousal, whereas the ability to do something allows the dissipation of emotional arousal.

The sustained arousal that is associated with emotional inhibition would therefore impose a chronic burden on visceral function and represent a risk factor for disease. 96

Figure 4. 97

Through influences on the neuroendocrine system, monoamine metabolism, and synaptic plasticity, innate immune cytokines and their signalling pathways can influence molecules that are believed to play a role in depression.
Mechanism
CRH (corticotrophin-releasing factor) is contained in neurons that are located in the hypothalamus, hippocampus, amygdale and cortex. These neurons form a circuit which, when activated by stressors, coordinate the stress response (including behavioral changes associated with anxiety).

Stress and emotions
Stress and emotions can have an impact on health through several pathways:
- Biological pathways: responsible for the effect of stress and emotions on visceral functions and the neuroendocrine system
- Sociobehavioral pathways
- Cognitive pathways

Stress and immunity
The effects of stress on immunity depend on the immune response, and a given stressor can either suppress or enhance different immune responses in the same individual.

Figure 5.  
There are many factors that can lead to activation of the innate immune response, which is characterized by increases in a variety of immune mediators that can be measured in the peripheral blood. These immune mediators can then interact with pathways known to be involved in the pathophysiology of depression.

Although the immune system has long been viewed as a self-regulated system, there is now evidence in favour of the existence of anatomical and functional relationships of this system with the brain.  

Authors: Rianne Engel & Joline Schilder
3.4.4 Depression

The similarity between the symptoms of cytokine induced sickness behavior and depression is striking (Figure 6a).

Overlapping symptoms of sickness behavior and major depression:

<table>
<thead>
<tr>
<th><strong>Sickness behavior</strong></th>
<th><strong>Major depression</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhedonia</td>
<td>Anhedonia</td>
</tr>
<tr>
<td>Anorexia (a)</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>Decreased libido</td>
</tr>
<tr>
<td>Cognitive disturbance</td>
<td>Cognitive disturbance</td>
</tr>
<tr>
<td>Psychomotor retardation (a)</td>
<td>Psychomotor retardation</td>
</tr>
<tr>
<td>Fatigue (a)</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Weight loss (a)</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>Increased pain complaints</td>
</tr>
<tr>
<td>Social isolation</td>
<td>Social isolation</td>
</tr>
<tr>
<td>Sad mood</td>
<td>Sad mood (b)</td>
</tr>
<tr>
<td>Worthlessness/guilt</td>
<td>Worthlessness/guilt (b)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Suicidal ideation (b)</td>
</tr>
</tbody>
</table>

(a) More frequent in sickness behavior than depression.
(b) More frequent in depression than sickness behavior.  

Figure 6.

The similarity between sickness and depression is only partial, whereas sickness is an adaptive response to infection by pathogens and fully reversible once the pathogen has been cleared, this is not the case for depression.
It is possible that depression represents a maladaptive version of cytokine-induced sickness, which could occur when activation of the innate immune response is exacerbated in intensity and/or duration, or that takes place in the context of an increased vulnerability to depression, for example, in individuals with hyperactive corticotrophin-releasing factor (CRH) neuronal circuits.

Pathway
Proinflammatory cytokines can cause depression by several mechanisms, for example the activation of IDO. The development of sickness behavior requires activation of pro-inflammatory cytokine signalling in the brain in response to peripheral LPS (Figure 6b). Some of the pro-inflammatory cytokines that induce sickness behavior also enhance activity of the ubiquitous indoleamine 2,3 dioxygenase (IDO). Activation of IDO results in decreased tryptophan (TRP) levels and increased production of kynurenine (KYN) which results in depression like behavior.\(^{101}\)

Patients with major depression have been found to exhibit evidence of an activated innate immune response as reflected by increased biomarkers of inflammation, including innate immune cytokines, acute-phase proteins, chemokines, and adhesion molecules. Innate immune cytokines have been shown to influence virtually every pathophysiological domain relevant to depression including monoamine neurotransmission, neuroendocrine function, synaptic plasticity, and regional brain metabolism.\(^{102}\)

Anatomical basis
The search for a possible neuroanatomical basis of cytokine induced depression has focused on the brain circuits that are involved in emotion processing and psychomotor retardation, both of which are altered in patients with clinical depression. Neuroimaging data of clinically depressed patients show decreased baseline activity in the frontal and temporal cortex and the insula, and increased activity in the cerebellum, subcortical and limbic regions. The neurobiological mechanisms underlying the behavioral effects of proinflammatory cytokines have rarely been investigated in enough detail to be able to relate a given behavioral effect of a cytokine to a specific action in a well-defined area(s) in the brain.\(^{103}\)
3.5 Conclusions

In studies of pain experiences, researchers are mainly focused on brain systems discussed in Chapter 1 and 2. The last decade the immune system, in particular the innate immune system, seems to have a major role in pain experiences.

The innate immune system can be chronically activated by non immune stimuli (like stress and other emotional states), and thereby cause disorders. This link between emotions and the immune system can be a bidirectional pathway. Shown in Chapter 2 emotions itself can cause different brain states that can result in pain experiences. The hypothesis of this review is that the brain states discussed in Chapter 2 can be linked with the immune system from this Chapter. Bodily states, emotional states and psychological dispositions can be the result of alterations in brain functions caused by still undetectable alterations in immune functions. It is time to seriously question whether and how stress and emotions cause disease.
Chapter 4.
Integration of brain systems in physical therapy
4.1 Introduction

Many physiotherapists make a living out of decreasing pain. Aside from the staple strategies, like movement, joint mobilisation and TENS, it is also known that motor imagery and mirror therapy and carefully explaining the biology that underpins someone’s pain state, can decrease pain.

What is not known, however, is how the brain contributes to the effects of physiotherapy interventions on sensory and motor maps and the immune system. Appropriate collaborations might make professionals reinterpret established effects.

Collaborative studies, between brain imagers, pain scientists and physiotherapists would stand to bridge this substantial gap in our knowledge. New treatments could tease out effects on sensory-discriminative, affective-motivational mechanisms, and innate immune responses.

In this Chapter different interventions are described in their current use. Additionally the authors give suggestions for other/reinterpreted targets of these interventions. Interventions are divided in:

- Possible therapeutic influences on sensory/motor body maps, and mirror neurons
- Possible therapeutic influences on the immune system

The authors try to give a new perspective on the possible future interventions in physical therapy. Finally meditation turns out to be an important mediator in keeping the body balanced.
4.2 Possible therapeutic influences on sensory/motor body maps, and mirror neurons

Persistent pain and cortical reorganisation are related, but we do not know whether one causes the other. There is emerging evidence that treatments that aim to normalise cortical organisation, also reduce pain and disability in people with chronic pain. For example, sensory discrimination training for phantom limb pain and tactile discrimination training for complex regional pain syndrome, both target body maps in primary sensory cortex and both show a clear relationship between increased tactile awareness, which is a marker of primary sensory cortex organisation, and decreased pain.

4.2.1 Physical examination

Current use
Physical examination is used for diagnosing disorders. Physical therapists use it every day to make sure their treatment is well adjusted.

Other targets / reinterpretation
Physical examination includes exhaustive and often repetitive provocation and mobilisations of specific joints. It requires the patient to carefully attend to and discriminate the location, quality and intensity of the percept. This works via similar mechanisms as discrimination training.

Concluded: It can be possible that physical examination starts a remapping process that has influence on abnormal sensory cortices (that occur in chronic pain patients).

4.2.2 Massage

Current use
Massage is the manipulation of superficial layers of muscle and connective tissue to enhance the function and promote relaxation and well-being. For example massage is used to relax high toned muscles in low back pain or to increase the flow of lymph in sportsmen after a work out. But such effects are yet to be supported by clinical studies.

Other targets / reinterpretation
The effect of massage on the somatosensory cortex is unknown, but it is likely that the somatosensory cortex also is stimulated with massage. During massage the patient is attending to the location and is discriminating the location that is touched.

Concluded: Via massage therapy a remapping process can be started and abnormal sensory cortices (that occur in chronic pain patients) can be normalized.
4.2.3 Motor imagery

Motor imagery is the mental representation of movement without any body movement. Motor imagery (MI) represents the result of conscious access to the content of the intention of a movement, which is usually performed unconsciously during movement preparation. Conscious motor imagery and unconscious motor preparation share common mechanisms and are functionally equivalent.

During motor imagery, no signals are sent to the muscles. Instead, they pass through a brain circuit that mimics the motor action and the brain experiences a faithful copy of the movement. Imaging a movement activates exactly the same brain regions that become active during real play minus the primary motor cortex.

Physical practice versus motor imagery

Contrary to the conditions in which a motor task can be learned implicitly with physical practice, mental practice with MI requires that subjects have all the necessary knowledge about the different components of the task before practicing. However, as with physical practice, the rehearsing of the task with MI can also give access to the non-conscious processes involved in learning the skilled behavior. Mental practice using MI training results in motor performance improvements:

- Training by using imagery techniques improves the strength of an isometric movement with 22% in a 4 week training period.
- Training by using physical practice improves the strength of an isometric movement with 30% in a 4 week training period.

In motor imagery no increase in muscle mass has been observed, the increasing strength may be caused by adaptive changes in the central processes in the brain. It has also been reported that MI improves the dynamics of motor performance. The lower effect of MI training compared to physical training may be caused by lacking sensorimotor feedback which results in decreased progress in motor training in patients.

Motor imagery improves motor training in healthy volunteers and patients. It can be seen as a complementary technique to execution training but should not be used as a substitute to physical practise.

Current use

Motor imagery is an accepted procedure in the preparation of athletes. Such practice usually covers a warming up period, relaxation and concentration, and then mental simulation of the specific movement. Motor imagery is also widely used as a technique to enhance motor learning and to improve neurological rehabilitation in patients after stroke.

Other targets / reinterpretation

It would be of interest to combine MI-training with physical practise. This would offer the opportunity to add additional training effects, start training earlier (even in a plegic state).
and provide a training method which could be performed by the patient alone after some instructions.
In order to increase the effect of imagery training compared to physical training, sensory feedback should be provided to the patients (like passive movements by the therapist).

Concluded: The brain is plastic, it can adaptively reconfigure itself in response to novelty, practice and damage. So a logical step will be to use motor imagery to try and drive plastic changes in the primary sensory and motor maps in chronic pain patients. This to give the brain an opportunity to encode successful sequences of movement. For example the imagery of smooth and pain-free movements.

4.2.4 Mirror therapy

Mirror therapy is a typical approach that involves placing one limb behind a mirror that is situated along an observer's midline. The observer who looks at the mirror's surface will perceive the reflected limb to be the limb that is hidden behind the mirror. People subjectively report the experience of seeing through the mirror's surface, as though it were actually transparent (Figure 1).

When patients move their good limb, they see two healthy limbs. This visual/ proprioceptive feedback from this experience can often reset the body map representation of the compromised limb. Muscle and joint maps become normal again and the brain is tricked into resetting the body maps. The motor-sensory mismatch can be broken by mirror therapy and pain can go away.

Current use

Mirror therapy is currently used in stroke rehabilitation, to relieve phantom limb pain and to relieve pain in the complex regional pain syndrome (CRPS).

Other targets / reinterpretation

That looking in a mirror does impact on sensory and motor processes raises the possibility that mirrors might help relieve pain in yet unconsidered conditions, for example dystonia.

Concluded: Mirror therapy, is probably no better than motor imagery for immediate pain relief, although it is arguably more interesting and might be helpful if used regularly over an extended period.
The relative dominance of visual input over somatosensory input suggests that mirrors might have utility in pain management and rehabilitation via multisensory interactions. Mirrors may still have their place in pain practice, but scientists should be open-minded as to exactly how. There is a need to critically question the theoretical bases for mirror therapy so that scientists might also come closer to determining who will benefit and who would not.
4.2.5 Altered movements

Targets
Imagined movements activate many of the same brain areas as actual movements (discussed in Motor imagery). If an individual thinks about a movement which is painful, or watches someone else perform that movement, motor neurons in the brain will be activated. When pain is chronic and severe, even imagined movements can be painful. A solution for this is to ‘trick’ the body maps in the brain. The same movement can be performed, but in another position. For example: turning the head. Sit on a swivel chair, look at a fixed object and rotating the body while looking at the fixed object. 108

Concluded: By performing altered movements other body maps are activated than the ones that are activated during painful movements. Because of the different movements it is possible to break through the system that causes the pain experience.

4.2.6 Physical exercise

Current use
It is well known that physical exercise is healthy for body and brain. Regular exercise offers protection against all-cause mortality, primarily by protection against cardiovascular disease and Type 2 diabetes mellitus.

Other targets / reinterpretation
But does physical exercise has a healing factor in chronic pain-patients? And if yes, how? The somatosensory cortex was shown to be activated by physical exercise in humans even if it is only imagined (see Motor Imagery). 109 The lower effect of MI training compared to physical training may be caused by lacking sensorimotor feedback. In physical exercise the sensorimotor feedback is supplied and therefore the total sensorimotor system is activated.

Concluded: Physical exercise improves the dynamics of motor performance. So if someone trains well and regularly this can result in well discriminative body maps and abnormal cortices are being normalized.
4.3 Possible therapeutic influences on the immune system

Recent treatments not only influence above described body maps and mirror neurons, but also have their effects on the immune system. Below the effects of different therapies on the immune system are discussed.

4.3.1 Endorphin production

Endorphins are endogenous opioid polypeptide compounds. They are produced by the pituitary gland and the hypothalamus in vertebrates during strenuous exercise, excitement, pain (decreasing pain) and orgasm. They resemble the opiates in their abilities to produce analgesia and a sense of well-being. Endorphins work as natural pain relievers. They can be found in more than twenty different parts in the body, such as the pituitary glands as well as in many parts of the brain and nervous system. \(^{110}\)

During emergency situations, endorphins can act within the dorsal horns to prevent pain messages from ever reaching the brain. This is highly adaptive when pain from tissue damage may hinder success in escaping life-threatening situations. \(^{111}\)

Endorphins may have a role in preventing obesity, diabetes and psychiatric diseases. Athletes also produce high levels of endorphins. \(^{112}\)

Targets

When someone has chronic pain or is depressive, the immune response can be disturbed (shown in Chapter 3). The production of cytokines maintains and the patient feels sick. Endorphins work as natural pain relievers and can ensure that the disturbance in the immune response is reduced.

Concluded: Performing exercise, having sex or even by eating chocolate, endorphins are produced and can thereby reduce the sickness behavior.

4.3.2 Massage

Touch is humans first language. The first system to function is touch, it mediates the humans experiences in this world. It makes one nourished, calmed, and one first become attached to others through touch. The sensation of touch is, in fact, the oldest and most primitive expressive channel, and a primary system for making contact with the external world. Humans are extremely dependent on touch until language, motor skills, and cognitive processes develop and can guide one in experiencing and interacting with the environment.

Touching involves risk. It is a form of nonverbal communication and therefore may be misunderstood by one or both parties involved. It invades intimate space and may be a threat. If one is not tuned with itself and the one we touch, it may be inappropriate. However, non-touch may be just as devastating at a time.
Targets

The effects of touch are hard to isolate. There are three theories that explain the benefits of massage and its impact on pain reduction: the endorphin-serotonin, the gate and the sleep deficit theories.

- The endorphin-serotonin states that massage stimulate the release of endorphins, these are the body’s natural pain suppressors.
- The gate theory is based on the idea that pain travels on the nerves to the brain and that one can overwhelm the nerves with other stimulation such as pressure (massage) or cold temperature and block the pain message. This is because pain fibers are shorter and less myelinated than pressure and cold temperature receptors. The brain receives the pressure or cold stimuli before the pain stimulus, the gate is closed, and the pain stimulus is not processed.
- The quiet or restorative sleep theory is based on the idea that during deep sleep, somatostatin is normally released. Without this substance, pain is experienced. Another substance called ‘P’ is released when an individual is deprived of deep sleep, and this substance is notable for causing pain. Thus, if a person is deprived of deep sleep, they may have less somatostatin and increased levels of Substance P. Massage therapy has been shown to improve sleep in several studies.  

Concluded: Massage has different ways to influence the brain and the immune system and thereby pain experiences. But these are just theories and more research is required.

4.3.3 Physical exercise

Physical exercise is normally used to increase muscle strength, condition, proprioception and to decrease body weight and the chance of health problems. But physical exercise also has effects on the immune system.

Targets

During exercise, IL-6 is produced by muscle fibers. IL-6 stimulates the appearance in the circulation of other anti-inflammatory cytokines and inhibits the production of the pro-inflammatory cytokine TNF-α (Figure 2). Which means the sickness response is reduced.

Figure 2

In infection (A), the cytokine cascade within the first few hours consists of TNF-α, IL-1α, IL-6, IL-1ra, TNF-R, and IL-10. The cytokine response to exercise (B) does not include TNF-α and IL-1 but does show a marked increase in IL-6, which is followed by IL-1ra, TNF-R, and IL-10.
Concluded: Physical exercise stimulates the production of anti-inflammatory cytokines and can thereby reduce the pain experience. It also reduces the sickness response during depression or other chronic problems.

4.3.4 Education and understanding
When a chronic pain-patient thinks that pain reflects the body state, the patient would do everything to avoid the pain. This means less or adapted movement, which at its turn can cause or maintain chronic pain. And if there is fear (for pain / more tissue damage), the central nervous system and immune system will be sensitized, which also can cause more pain.

Current use
Education and understanding is currently used by physical therapists to make sure that patients completely understand what is going on in their body and why certain actions must or can’t be performed. If a patient understands why an exercise must be performed, it is more likely that the patient is committed to the therapy.

Other targets / reinterpretation
Another way to look at education and understanding is to look at the effects of beliefs and emotions. Beliefs and emotions can trigger the sickness response. But they can also make one well. When someone expects a medical treatment to work, their body releases pain killing substances and their mind starts to interpret symptoms differently. All therapies can work if the patient puts its faith in it.\textsuperscript{115}

Concluded: If a patient understands that pain doesn’t always mean that there is tissue damage, the perceived threat will be reduced. This means the central nervous system will be less activated. In addition, when a patient isn’t afraid to move because of the pain, he will do his exercises which help him to recover.\textsuperscript{116}
Finally, it is important to make sure patients are motivated and are willing to put faith in the therapy.
4.4 **Meditation**

When people enter deep meditation or trance, they say that their bodies and minds expand out into space. Body awareness fades, and they are left with a diffused and non localized sense of themselves. In the brains of people who meditate, activity in the parietal lobes appears. This means the dissolution of the bodily self accompanies the shutting down of the body maps that create it. Active awareness of internal sensations can lead to amazing results. Meditators like yogis and lamas actually gain control over their heart rates, oxygen consumption, and other basic autonomic functions. They feel emotionally stable. 117

In a study in the effect of meditation on chronic pain, the pain acceptance (measured with the Chronic Pain Acceptance Questionnaire) total score significantly improved for the group that meditates, while the control group worsened over the 8-week period. 118

4.4.1 **Brain regions**

During meditation different brain regions light up in MRI scans.

- Meditation exerts control over both pain and emotion. People who practise meditation for 30 years show a 40-50% lower brain response to pain compared with healthy controls.
- Meditation is also capable of calming the right frontal insula. Activation of the insula results in feeling emotions. So by calming the insula emotions become weakened.
- An experienced meditator shows structural brain changes. The right frontal insula and the left prefrontal cortex (associated with feelings of joy and happiness) are larger and thicker in meditators.

Concluded: In meditation brain regions that are involved with pain and emotion are less activated, whereas brain regions that are associated with happy feelings are more developed. So tuning up the body maps of the right frontal insula via meditation may turn out to be a good investment to create a balanced body state. 119
4.5 Conclusions

All treatments discussed in this Chapter can have different effects on brain systems and/or the immune system. Evidence for the effects of the treatments varies. It is important to keep in mind the already proven effects of the treatments on the brain. If physical therapists know these effects on the brain, they are able to treat their patients more efficient.

Science stands to discover what the established effects of different treatments are on the brain. Treatments like: massage, physical exercise, motor imagery, mirror therapy, altered movements, education, and meditation. This will provide fresh targets for physical therapy.

All involved professionals (pain scientists, brain imagers and physiotherapists) must be sufficiently open-minded to consider new explanations for old effects, and sufficiently alert to pursue new and better treatments.
Final conclusion

There are several systems that can explain the maintenance of chronic pain. The systems in this review include: The mirror neuron system, Body maps and their plasticity and the Innate immune system. In all these systems emotions seem to have a greater influence on chronic pain.

Because of different studies it has become clear that behavior, perception, and movement all have their specific effects on brain areas. These specific effects can open new doors in physical therapy. However, more research is required to make sure what the exact effects are on the brain. Because, up until now mainly explorative and experimental researches are performed.

It is important to keep in mind the effects of different treatments on the brain. This because damage or wrong alterations are easily made. If science has a clearer image of how different brain systems are connected with each other, how they can be influenced, and which role emotions play in this image, a new door opens to develop other or re-integrated ways to treat chronic problems.

The message of this review is:

“Listen carefully to your patients, and use your common sense!”
References

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113 G. Gray. The Roles Of Touching And Massage Among Occupational Therapists And Teachers In Early Intervention Programs. Auburn University. 2008.