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## Emotions Studied by Imaging of the Human Brain

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# Emotions Studied by Imaging of the Human Brain: The Somatic and Emotional Motor Systems

# 95

Gert Holstege and Hieu K. Huynh

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## Abstract

The brain has only two goals, survival of the individual and survival of the species. One of the most important tools to accomplish these goals is the motor system, which includes the somatic or voluntary motor system and the emotional motor system (EMS). The EMS is equally or even more important than the somatic motor system. In humans, the cortex cerebri with the corticospinal tract plays the most important role in the somatic motor system, while in the EMS, the periaqueductal gray (PAG) plays a central role controlling nociception, cardiovascular changes, respiration, micturition, parturition, defecation, vocalization, vomiting, coughing, sneezing, mating behavior, pupil dilation, and defensive posture.

## Keywords

Blood pressure · Breathing · Defecation · Dopaminergic cell group · Emotional motor system (EMS) · Heart rate control · Micturition · Motor cortex · Parturition · Periaqueductal gray · Red nucleus · Sexual activity, posture necessary for · Sexual intercourse, in humans · Somatic motor system · Speech · Ventromedial medulla

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## Brief History

Many neurologists think that the so-called corticospinal tract is the most important part of the motor system because numerous patients suffer from lesions of the corticospinal tract. For example, an infarction on the left side in the white matter (internal capsule) interrupts the corticospinal tract leading to great problems with voluntary movements on the right side and vice versa. Since internal capsule lesions interrupting the corticospinal tract are not exceptional at all, most neurologists think that this tract is the main component of the motor system. Although, indeed, in humans the corticospinal tract is a crucial component of the somatic or voluntary motor system, the emotional motor system (EMS) is an equally or even more important part of the motor system.

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## Introduction

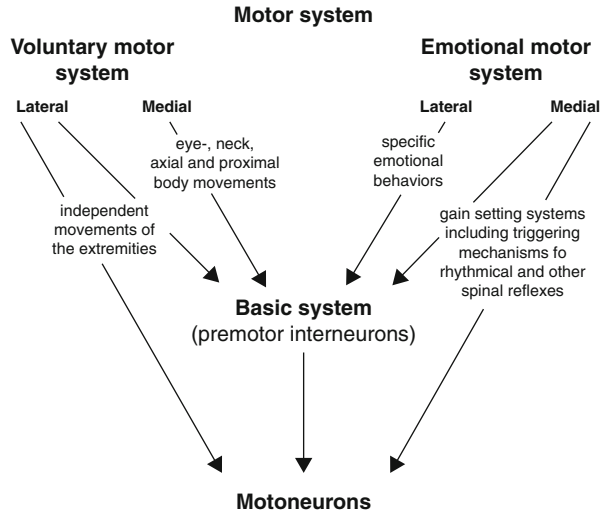
The brain has only two goals, survival of the individual and survival of the species. The most important tool to accomplish both goals is the motor system. Many neurologists think that the so-called corticospinal tract is the most important part of the motor system because numerous patients suffer from lesions of the corticospinal tract. For example, an infarction on the left side in the white matter (internal capsule) of the cortex of an individual interrupts this tract leading to great problems to produce voluntary movements on the right side and vice versa. As the word says, the corticospinal tract originates in the cortex and terminates in the spinal cord. Since internal capsule lesions interrupting the corticospinal tract are not exceptional at all, most neurologists think that this tract is the main component of the motor system. In reality, this is not the case. Although, indeed, in humans the corticospinal tract is a crucial component of the somatic or voluntary motor system, the *emotional motor system (EMS)* (Holstege 1992) is an equally important or perhaps even more important part of the motor system (Holstege et al. 2004) (Fig. 1).

## The Somatic or Voluntary Motor System

### Motoneurons in Spinal Cord and Brainstem

As mentioned above, the corticospinal tract in humans is a crucial component of the somatic motor system. Fish, however, do not have a corticospinal tract but still move through the water smoothly using coordinated muscle movements. This coordination is not processed by the cortex, as in humans (see below), but by the brainstem. The cells that innervate and activate the muscles in fish as well as in all other vertebrates including humans are called motoneurons, located in the spinal cord and brainstem. Each muscle is innervated by a distinct group of motoneurons. However, such a group does not decide by itself when to generate muscle movements and when not. Even the so-called premotor interneurons, usually located close to the motoneuronal cell groups, do not decide when to excite their motoneurons but receive instructions

**Fig. 1** The motor system consists of a somatic or voluntary and an emotional motor system. Both consist of a medial and a lateral component, but all make use of the motoneurons and their premotor interneurons. Please note that motoneurons not only meant somatic motoneurons innervating the striated muscles but also the so-called sympathetic and parasympathetic preganglionic motoneurons in brainstem and spinal cord



from other areas in the central nervous system (CNS). Their major task is to excite the motoneurons of the agonist muscle and inhibit the motoneurons of the antagonist muscle in order to prevent a simultaneous opposite movement. Therefore, even in fish, the decision whether or not to activate a certain muscle in the context of moving to another site in the water is not taken by neurons in the spinal cord but at a higher level in the lower or caudal brainstem. The lowest or most caudal part of the brainstem is a rostral extension of the spinal cord, which continues laterally as the lateral tegmental field. This lateral tegmental field, similar to the spinal cord, contains motoneurons with their premotor interneurons innervating the muscles of the head, such as tongue, throat, mouth, face, and chewing muscles (Holstege et al. 1977) (Fig. 2). The sensory part of the spinal cord, the dorsal horn, also extends rostrally in the lateral brainstem, where it is called trigeminal nucleus.

**Medial Component of the Somatic Motor System**

In fish, the neurons that coordinate the movements in order to move through the water are located dorsomedially in the lower brainstem, in the so-called dorsomedial medulla (Mullins et al. 2011). Ventral to the dorsomedial medulla is the ventromedial medulla, which plays a role in the EMS (see later). The neurons in the dorsomedial medulla of the fish send fibers throughout the length of its spinal cord to inform the motoneurons and their premotor interneurons when to fire. This relatively simple system works fine, since fish move smoothly through the water and are able to escape threats as larger fish that want to catch and eat them. The neurons in the dorsomedial medulla determine which direction the fish has to swim, but they, in turn, receive instructions from more rostral regions in the brainstem. These neurons are informed about the circumstances in the environment by the visual system. In fish, the visual system is not, or to only a very limited extent, able to recognize

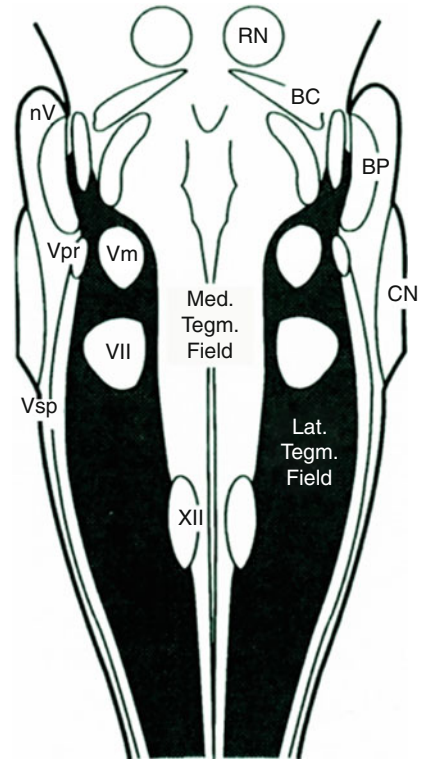


**Fig. 2** On the *left*, the lesion in the left brain of a patient in that part of the motor cortex that controls face musculature. The lesion caused inability of moving the face muscles on the contralateral side, when asked to show her teeth (*middle*). However, when told a funny story, the patient is still able to smile, using the EMS to contract her facial muscles (*right*)

objects the way humans do, but it distinguishes changes in the visual field and determines whether these changes are large or small. When the changes are large, it might represent a large moving object such as a large fish that wants to eat the smaller fish. Large movements in the visual field, therefore, are interpreted as dangerous. The rostral brainstem cells of the fish, receiving this information, will then generate a flight response by giving orders to the muscles of the body via the dorsomedial medulla. In contrast, in case the moving object is smaller than the fish, it will try to catch and eat it. In that case, the movements will be organized in such a way that the fish approaches the smaller moving object. Despite the simplicity of this brainstem organization, it seems to work well, since fish still exist. Fish have no limbs, which explains why the dorsomedial medulla only controls axial and proximal muscles. In further phylogenetic development, many more sophisticated body parts develop such as limbs, but the dorsomedial medulla continues to control axial, proximal, and neck musculature (Fig. 3, left) as in fish, and it still has this function in further developed vertebrates including humans (Holstege 1988a).

Axial and neck musculature control not only body posture but also the position of the head on the trunk, thus the position of the visual field. Other muscles that are involved in visual field control are the extraocular muscles, which, in fish, produce only horizontal eye movements. The motoneurons innervating these muscles are also controlled by neurons in the dorsomedial medulla, which is the reason that they located in this same area. This motoneuronal cell group is called nucleus abducens. Thus, neurons in the dorsomedial medulla control head and eye position, i.e., the position of the visual field. Later in the phylogenetic development, eye muscles evolved that generate vertical eye movements. For this reason, the cell groups involved in vertical eye movement control are located further rostrally in the

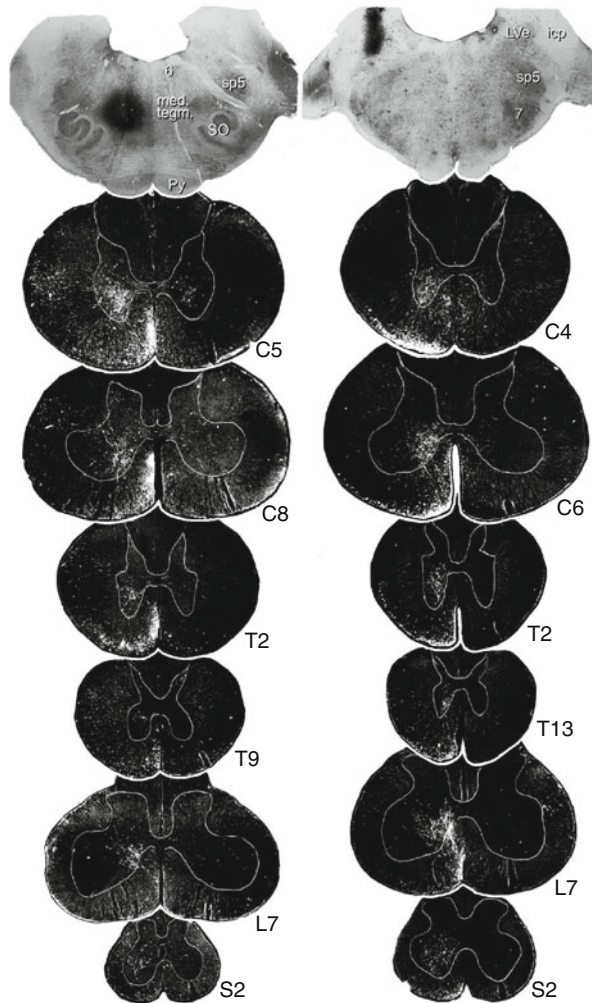
**Fig. 3** The caudal brainstem consists of a lateral tegmental field (*black*) with motoneurons and premotor interneurons and a medial tegmental field, which consists of a dorsal and a ventral medial medulla. *Vm* motor trigeminal nucleus, *Vpr* principal trigeminal nucleus, *Vsp* spinal trigeminal tract and nucleus, *VII* facial nucleus, *XII* hypoglossal nucleus, *BC* brachium conjunctivum, *BP* brachium pontis, *CN* cochlear nuclei, *nV* trigeminal nerve, *RN* red nucleus



brainstem than those controlling horizontal eye movements. Examples of cell groups controlling vertical eye movements are the interstitial nucleus of Cajal, which control the position of the eyes in a vertical plane, and the rostral interstitial nucleus of the MLF that coordinate eye movements in the vertical plane. Since control of only vertical eye muscle movements is not sufficient for controlling the position of the visual field in the vertical plane, both cell groups also send fibers to the neck and axial muscle motoneurons in the spinal cord in order to coordinate head and eye position in the vertical plane.

Another group of neurons involved in visual field control comprises the vestibular nuclei because they receive information from the vestibular organs about the position of the head. They also have access to eye muscle motoneurons and their premotor interneurons via the medial longitudinal fasciculus (MLF) (Zwergal et al. 2009) as well indirectly via the cells in the dorsomedial medulla (Peterson and Abzug 1975). Also, the vestibular nuclei have direct access to the motoneurons and their premotor interneurons of the axial and head muscles in the spinal cord (Fig. 4, right). The vestibular nuclei use two pathways, the medial vestibulospinal tract that specifically controls neck muscles and the lateral vestibulospinal tract that coordinates axial as well as neck movements, because it descends throughout the length of the spinal cord (Holstege 1988a).

**Fig. 4** *Left*: After an injection of  $^3\text{H}$ -leucine as a general tracer in the medial tegmentum of the pons, rostral to the ventromedial tegmentum, the medially descending pathways can be observed in dark field throughout the length of the spinal cord. On the *right*, a very similar projection is seen when the tracer is injected in the lateral vestibular nucleus. 6 abducens nucleus, 7 facial nucleus, *icp* inferior cerebellar peduncle, *LVe* lateral vestibular nucleus, *med. tegm.* medial tegmental field, *Py* pyramidal tract, *sp5* spinal trigeminal nucleus, *SO* superior olivary complex



Albeit that, in humans, the medial component of the somatic motor system is largely organized by the cortex, the dorsomedial medulla in the brainstem is still functional because of its connections with the vestibular nuclei, spinal cord, and eye muscle motoneurons. The motor cortex part involved in steering proximal and axial muscles has strong connections with the dorsomedial medulla. In simple terms, when a control center in the CNS is functioning well, there is no phylogenetic reason to replace it by other (cortical) structures. In fact, not only in fish but also in humans, the dorsomedial medulla still plays a crucial role in the control of posture in general and the position of the visual field in particular. As we will see later, the EMS in humans also uses caudal brainstem cell groups that function properly at a basic level.

## Lateral Component of the Somatic Motor System

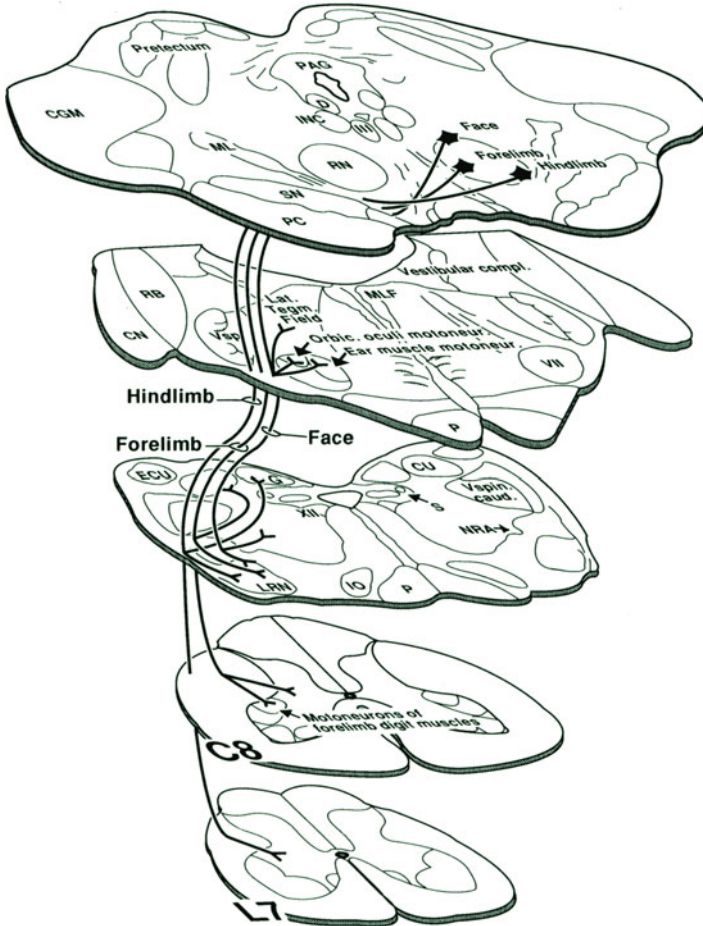
### Red Nucleus

Since it was phylogenetically advantageous to move from the sea to the land, fish developed limbs. As with vertical eye movement control (see above), the neuronal cell groups coordinating limb movements evolved later, thus further rostrally in the brainstem than the axial, proximal, and neck muscle control regions. This group of neurons, called magnocellular red nucleus, sends thick fast fibers to motoneurons and their premotor interneurons innervating limb muscles. In contrast to the dorsomedial medulla, the rubrospinal neurons are subdivided into different parts innervating different muscle groups. In simple terms, one might distinguish three different rubrospinal cell groups, one innervating face, mouth, and other oral muscles, located in the dorsal part of the red nucleus, one innervating the upper limb, located in the ventromedial red nucleus, and one innervating the lower limb, located in the ventrolateral red nucleus (Fig. 5). The red nucleus decides about limb movements, i.e., in which direction the animal is moving or when and how it reaches for food. The red nucleus receives afferent information from the cerebellum, motor and premotor cortex (Kuypers 1981; Holstege 1991), and from the serotonergic, noradrenergic, and dopaminergic level-setting systems (Huffman and Davis 1977; Bosler et al. 1983; Domyancic and Morilak 1997), as well as from the deep layers of the superior colliculus, (personal observation), where visual, auditory, and somatosensory information is processed.

### Motor Cortex

Without motor memory, it is impossible to generate complicated limb movements. Sufficient memory involves many premotor interneurons, for which, phylogenetically speaking, there was no room close to the red nucleus in the upper brainstem. The same was true for memory neurons for visual, auditory, and somatosensory systems. The phylogenetic solution was to copy the brainstem motor, visual, auditory, and somatosensory systems into the most rostral part of the developing central nervous system, the telencephalon. The result was a cerebral cortex with a primary motor, visual, auditory, and somatosensory cortex. Those parts of the primary motor cortex that generates limb movements can be considered as a copy of the magnocellular red nucleus and the part of the motor cortex that controls axial and proximal musculature as a copy of the dorsomedial medullary tegmentum. Nevertheless, in rats, the magnocellular red nucleus is still powerful in steering limb movements, although its motor cortex has more memory cells to produce certain movements. In cats, the corticospinal tract is further developed than in rats, although the rubrospinal tract, with its direct projections to distal forelimb muscle motoneurons (Holstege 1987a), is further developed than the corticospinal tract. In monkey, the corticospinal tract becomes more powerful and projects directly to motoneurons, and the number of memory neurons in the premotor cortex is more numerous than in cats (Holstege and Tan 1988; Ralston et al. 1988). The reason for the rubrospinal pathway to still play an important role in the motor system is also that the motor

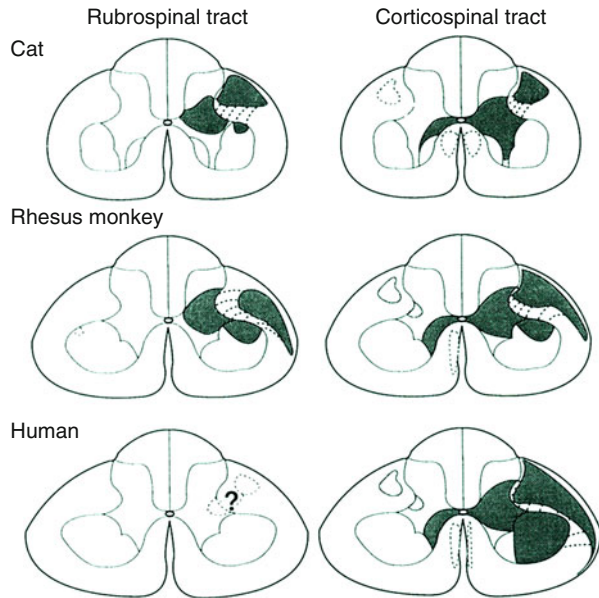




**Fig. 5** Schematic drawing of the rubrospinal tract. Note that the face, forelimb, and hind limb areas project to different parts of the brainstem and spinal cord. *III* oculomotor nucleus, *Vsp* spinal trigeminal tract and nucleus, *V spin. caud.* caudal spinal trigeminal nucleus, *VII* facial nucleus, *XII* hypoglossal nucleus, *CGM* corpus geniculatum mediale, *CN* cochlear nuclei, *CU* cuneate nucleus, *ECU* external cuneate nucleus, *G* gracile nucleus, *INC* interstitial nucleus of Cajal, *IO* inferior olive, *lat. tegm. field* lateral tegmental field, *LRN* lateral reticular nucleus, *ML* medial lemniscus, *MLF* medial longitudinal fasciculus, *NRA* nucleus retroambiguus, *P* pyramidal tract, *PAG* periaqueductal gray, *PC* pedunculus cerebri, *RB* restiform body, *RN* red nucleus, *S* solitary tract, *SN* substantia nigra

cortex, by way of strong projections to the rubrospinal cells, uses the red nucleus for generating limb movements (Kuypers 1958). In humans, however, the number of fibers of the motor corticospinal tract has become so much higher than the rubrospinal tract fibers that there was no further need for an operative rubrospinal tract, and the remaining number of rubrospinal neurons in humans has been estimated to amount around 300 (Nathan and Smith 1982), while in rats, cats, and monkey, rubrospinal neurons are much more numerous (Holstege 1991) (Fig. 6). It

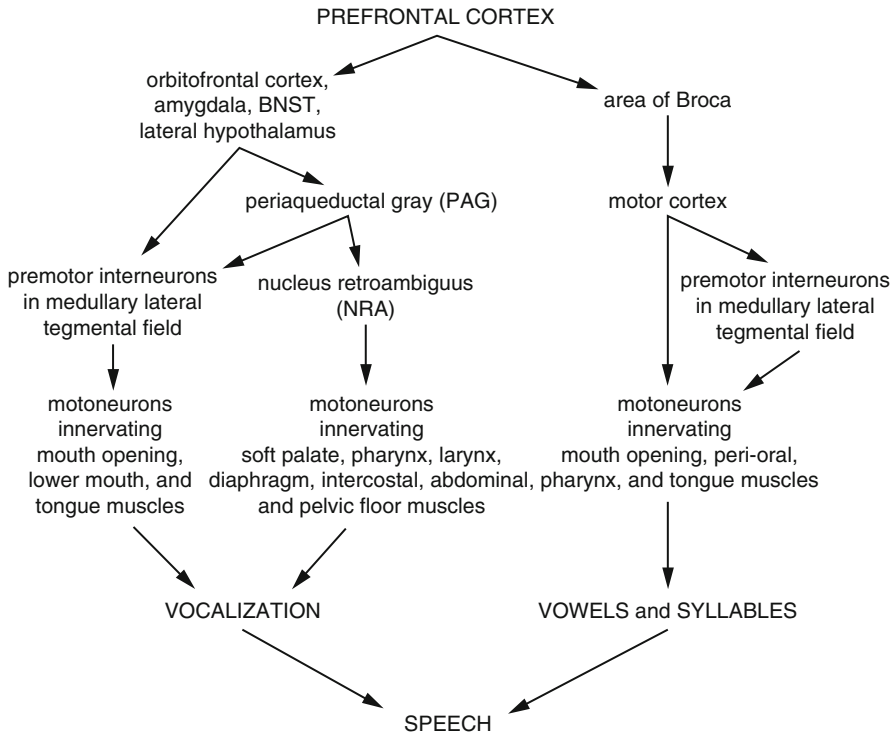
**Fig. 6** Schematic drawing of the rubrospinal and corticospinal tract in cat, rhesus monkey, and human. Note the strength of the rubrospinal tract in cat and monkey but the weakness or even absence of this tract in humans. Note also that the corticospinal tract gets stronger going from cat to monkey to humans



means that a lesion of the corticospinal tract in rats or cats, not involving the rubrospinal tract, does not affect the ability to move their limbs, because the rubrospinal tract takes over. In humans, a similar corticospinal tract lesion produces complete loss of the ability to move the contralateral body parts, of which the control of the most precise movements as those of distal limbs or mouth (Fig. 2, left) is affected most.

### Speech

The best examples of premotor interneurons in the cortex memorizing how to produce complicated movements are those involved in speech. These neurons are located on the left side in the so-called area of Broca. These cells remember how to produce very complicated movements of the mouth, cheek, soft palate, pharynx, and larynx in order to generate words and sentences. These Broca cells project to those neurons in the motor cortex that, in turn, project to the motoneurons and premotor interneurons in the caudal brainstem (Fig. 7, right). This pathway is called corticobulbar tract because the motoneurons involved are not located in the spinal cord, but in the bulbus or caudal brainstem or, more precisely, in the bulbar lateral tegmental field (Fig. 3). Neurons in the area of Broca are able to generate the word “table” and thousands of other words in different languages. However, the corticobulbar tract does not produce sound but modulates it, resulting in words and sentences. As we will discuss later, the sound production as such is a task of the EMS. In case the area of Broca on the left side is lesioned, the individual cannot produce complete sentences (motor aphasia) (see Alexander and Hillis 2008) but is



**Fig. 7** Summary diagram of the systems that produce speech. On the *left*, the EMS; on the *right*, the somatic motor system

still able to produce sound. However, when those parts of the EMS involved in sound production (see below) are lesioned, the individual becomes mute and cannot produce any sound, although the cortex and corticobulbar tract are intact (Esposito et al. 1999).

## The Emotional Motor System

Similar to the somatic motor system, the EMS has a medial and a lateral component. The medial component consists of neurons sending diffusely projecting pathways to the spinal cord as well as the cell groups that control the neurons that generate these diffuse pathways. The lateral component, on the other hand, consists of specific motor output systems that are under control of particular emotional brain regions.

### Medial Component of the EMS

As explained in previous paragraphs, the spinal cord consists of a motor part on the ventral side with motoneurons and premotor interneurons and of a sensory part on the dorsal side called dorsal horn. The latter part processes stretch-sensitive

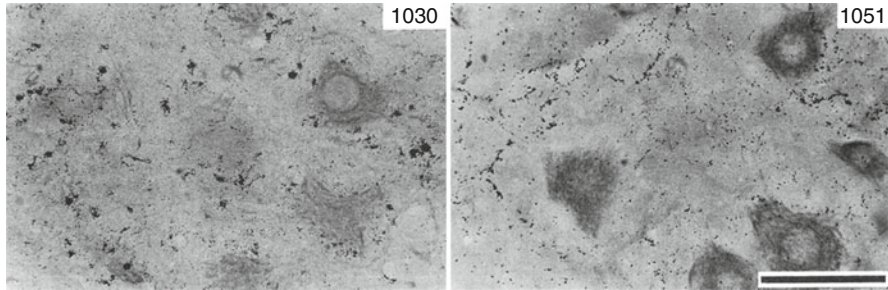
information from muscles and tendons and somatosensory information from skin through thick afferent fast-conducting fibers. This information is crucial for the motor system to coordinate muscle contractions. There are also thin slow-conducting fibers, which are hard to excite. Only stimuli that might be harmful or noxious to the individual are able to excite these fibers. Such information is called nociception, of which pain perception is the best example, but it also involves heat and cold.

### **Ventromedial Medulla**

Neurons in the dorsomedial medulla coordinate axial, neck, and external eye muscles. Neurons, located ventral to the dorsomedial medulla, i.e., in the ventromedial medulla, have a completely different function. They send fibers throughout the length of the spinal cord. Neurons in the caudal half of the ventromedial medulla send fibers to all somatic motoneurons and their premotor interneurons, as well as to all preganglionic sympathetic and parasympathetic motoneurons with their premotor interneurons. This projection is very diffuse; the fiber of one particular neuron gives off collaterals to the cervical as well as to the thoracic, lumbar, sacral, and coccygeal ventral horn (Huisman et al. 1981). The cells in the rostral half of the ventromedial medulla project to the neurons in the dorsal horn. Neurons located most rostrally in the ventromedial medulla project to laminae III and IV where nonnociceptive information is processed. Neurons caudal to these, but still in the rostral half of the ventromedial medulla, project specifically to neurons in Rexed's laminae I and V that are involved in processing nociceptive information (Holstege 1988b). Altogether, the neurons in the ventromedial medulla determine the so-called level setting of all spinal cord neurons in the dorsal as well as ventral horn. In simple terms, they determine the level of activation of these spinal neurons, i.e., determine the amount of energy that is needed by other, more specific systems to generate an effect. For example, electrical stimulation of cells in the rostral half of the ventromedial medulla results in complete disappearance of nociception or pain (Fields and Basbaum 1978).

### **Neurotransmitters in the Ventromedial Medulla**

There are several neurotransmitters that play a role in the level-setting system of the ventromedial medulla to the motoneurons in the spinal cord. Most well known is serotonin, which facilitates motoneurons possibly by acting directly on  $CA^{2+}$  conductance or indirectly by reduction of  $K^{+}$  conductance of the motoneuronal membrane and, thus, enhances the excitability of the motoneurons for inputs from other sources as the corticospinal tract (see above). Not all the diffusely projecting neurons in the ventromedial medulla contain serotonin as is often thought. Other peptides playing a role in these diffuse pathways to the spinal cord are substance P, thyrotropin-releasing hormone (TRH), somatostatin, methionine (M-ENK), and leucine-enkephalin (L-ENK), while some cells in the ventromedial medulla contain vasoactive intestinal peptide (VIP) and cholecystokinin (CCK). Several of these peptides coexist in the same cell with serotonin. Also acetylcholine, somatostatin, and even GABA play a role, which means that the diffuse pathways have facilitatory as well as inhibitory effects.



**Fig. 8** Bright-field photomicrographs of autoradiographs in a somatic motoneurons cell group in the lumbar 7 ventral horn in cats after injections of  $^3\text{H}$ -leucine in the ventral medial medulla. On the *left*, the injection was made in the ventral medulla not involving the raphe nuclei; on the *right*, the projection to the same cell group after an injection in the raphe pallidus. Note the differences in termination patterns, probably representing important differences in function. Bar represent 0.1 mm

In the cat, the termination of diffuse pathways that originate from regions with a great many serotonergic neurons differ from those of laterally adjoining regions that do not or only to a very limited extent contain serotonergic neurons (Fig. 8), see (Holstege 1991) for review. The serotonergic neurons in the ventromedial medulla send fibers not only to the spinal cord but also to the lateral medulla (lateral tegmental field) with motoneurons and premotor interneurons. Actually, the serotonergic neurons are located in various medial cell groups extending from the ventromedial medulla until the dorsal raphe nucleus in the mesencephalon. The more rostrally located serotonergic neurons project to all rostral regions of the CNS, e.g., to diencephalon and telencephalon, which means that all cortical regions receive serotonergic afferents.

### Afferent Projections to the Ventromedial Medulla

None of the more than 100 billion neurons in the CNS function by themselves but are always instructed by other neurons in the CNS. This is also true for the neurons in the ventromedial medulla. The strongest projection to the ventromedial medulla originates in the midbrain periaqueductal gray (PAG), but there also exist afferent projections from diencephalon, such as the medial hypothalamus and preoptic area (Holstege 1987b) as well as from the telencephalon (ventromedial orbitofrontal cortex) (Kuipers et al. 2006). Remarkably, only the rostral half of the ventromedial medulla, which sends fibers to the dorsal horn, receives afferents from more lateral parts of the limbic system, such as the lateral hypothalamus (Holstege 1987b), amygdala (Hopkins and Holstege 1978), and bed nucleus of the stria terminalis (BNST) (Holstege et al. 1985). Also the ventromedial orbitofrontal cortex projects to only that part of the ventromedial medulla. In conclusion, the ventromedial medulla contains a great many neurons with many different neurotransmitters and neuromodulators. Its rostral half controls the dorsal horn, its caudal half the ventral horn of the spinal cord. Both parts receive very strong connections from the PAG but the rostral half also from many higher level parts of the limbic system including the

medial orbitofrontal cortex. Through this pathway, these regions can have direct control of nociception throughout the body.

### **A5, A7, and A11**

The neurons in the ventromedial medulla are not the only ones that send diffuse pathways to the spinal cord. Others are the noradrenergic neurons in the locus coeruleus/subcoeruleus (A7 cell group) in the dorsolateral pons and A5 cell group in the caudal pontine ventrolateral tegmentum. Similar to the serotonergic neurons, also these neurons send fibers to all parts of the CNS from the frontal cortex to the coccygeal spinal cord. Unlike the serotonergic neurons that are located throughout the rostrocaudal extent of the brainstem, the noradrenergic neurons are exclusively located in the dorsolateral pons (locus coeruleus and subcoeruleus). The locus coeruleus receives afferents from the same areas as the ventromedial medulla, e.g., the PAG (Mantyh 1983), central nucleus of the amygdala, BNST, and lateral hypothalamus (Nieuwenhuys et al. 2008).

The third cell group that sends diffuse projections to the spinal cord is the A11 nucleus in the caudal hypothalamus containing dopaminergic neurons. There are many cell groups in the rostral brainstem that contain dopaminergic neurons, sending dopaminergic fibers to all parts of the CNS, but only the A11 cell group send fibers to all parts of the spinal cord (Holstege et al. 1996; Barraud et al. 2010). Also the dopaminergic A11 cell group receives afferents from many limbic structures as hypothalamus, PAG, insula, orbitofrontal cortex, amygdala, and BNST.

### **Role of the PAG in the Medial Component of the EMS**

As indicated by its name “periaqueductal gray,” the neurons of the PAG are located in the area around the aqueduct. The lateral border is formed by tectobulbospinal fibers that originate in the deep layers of the superior colliculus. The tectospinal fibers cross the midline already in the midbrain to further descend into the caudal brainstem and upper cervical cord. However, this lateral PAG border is artificial because the cells lateral to these tectospinal fibers are involved in similar functions as those within the PAG. The PAG, thus including the cells just lateral to it, is best known for its role in pain perception because electrical stimulation of the PAG in animals resulted in an almost complete disappearance of nociception. This observation led neurosurgeons to electrically stimulate the PAG in patients that suffered from extreme pain, e.g., caused by malignant outgrowths in different parts of the body. Although this PAG stimulation indeed eliminated the pain sensation in these patients, they also became very emotional and felt extreme fear, panic, anxiety, terror, or even feelings of immediate death (Nashold et al. 1969; Schvarcz 1975). In later studies, stimulation in more rostral parts of the PAG resulted in much better pain treatment, without the emotional feelings (Bittar et al. 2005). Nevertheless, the first PAG stimulations demonstrated that the PAG does not function exclusively as a pain inhibitory center but as a cell group that plays a central role in basic survival. One of these functions is changing the level setting in the spinal cord. For example, in a situation in which the individual is threatened by events in its immediate surroundings, e.g., a car driving in his/her direction or a person threatening him/her, it is

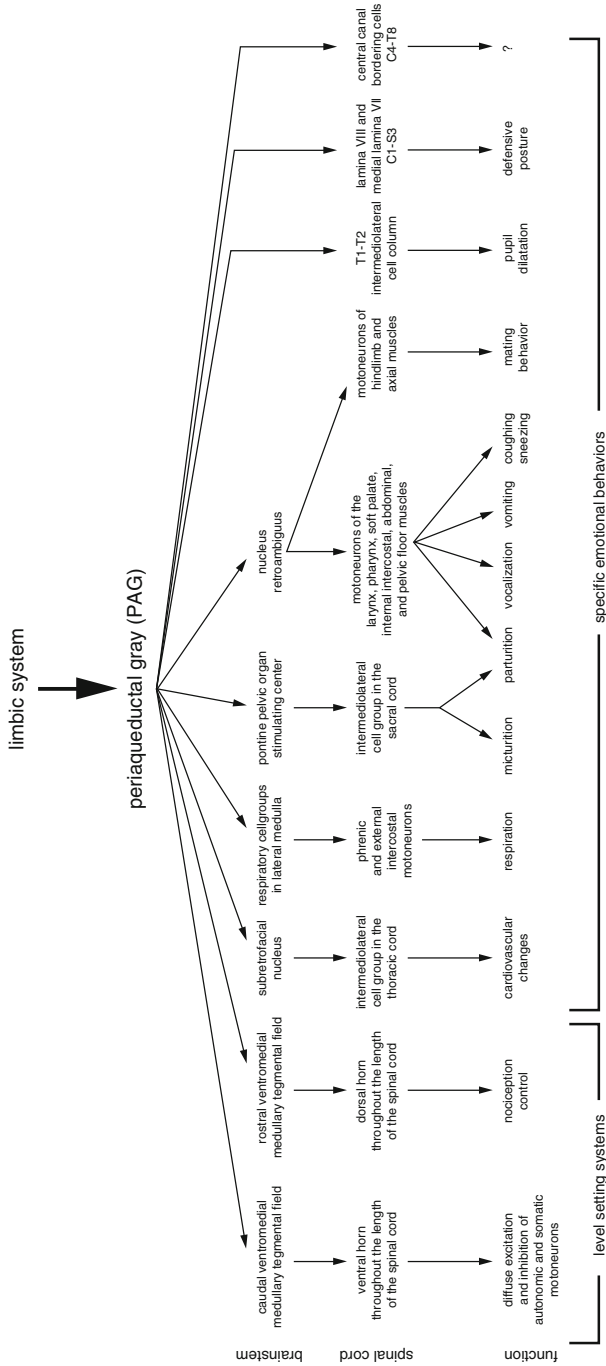
necessary to fight, flight, or fright, i.e., attack, flee, or freeze. It has been shown in cats with a permanent needle in the caudal PAG in a very relaxed situation that electrical stimulation resulted in a sudden attack of whatever person in its immediate surroundings, even when this person is known to the cat as nonthreatening and providing food (Bandler 1975). Terminating the PAG stimulation resulted in an immediate stop of this aggressive behavior. Stimulation in more ventral parts of the PAG in rats, on the other hand, resulted in immediate freezing behavior (Bandler and Keay 1996). These results demonstrate that the PAG is able to produce complete behaviors directly related to basic survival. The PAG, therefore, is used as a tool for higher level structures as amygdala, BNST, lateral hypothalamus, preoptic region, and, especially in humans, the medial orbitofrontal cortex and insula to generate basic survival behavior. Hence, although these regions play crucial roles in basic defensive mechanisms, they need the PAG to bring about the appropriate emotional behavior. Large lesions of the PAG usually results in the death of the individual or, in rare cases, in akinetic mutism, a situation in which the patient is breathing but no longer aware of his/her existence. In case of parenteral or intravenous nutrition, the patient may remain in this condition for 10 years or more. In such cases, the family members often decide to stop the parenteral nutrition in order to let the patient pass away.

### **Lateral Component of the EMS**

The PAG, which maintains such an essential position in basic survival, not only controls level setting including pain perception and motor output but also generates more specific motor outputs, which, together, constitute the lateral component of the EMS. Examples of such specific motor output systems are blood pressure and heart rate control, breathing, vocalization, vomiting, micturition, and parturition (Fig. 9).

### **Blood Pressure and Heart Rate Control**

“I love you with all my heart,” “from the bottom of my heart,” “broken hearted,” “learn by heart,” “accept Jesus in your heart,” “a heartfelt plea,” “break my heart,” and many other phrases suggest that the EMS is located in the heart instead of the CNS. It demonstrates the enormous impact of emotional processing on heart function. Obviously, events in the surrounding of the individual that are estimated by the brain as critical for survival of the individual or of the species call for an immediate response by the EMS. The heart is almost always involved in this response because the body needs more blood going to those parts that perform the necessary defensive actions as fight, flight, and fright. Therefore, there exist specific pathways from the dorsal and lateral PAG to the ventrolateral tegmental field just caudal to the facial nucleus, a region called retrofacial nucleus, that increase blood pressure and heart rate (Lovick 1985; Carrive et al. 1989; Hamalainen and Lovick 1997; Kubo et al. 1999), while the ventrolateral PAG generates a decrease of blood pressure and heart rate (Carrive and Bandler 1991), also in humans (Green et al. 2010; Pereira et al. 2010). Even stimulation on the orbitofrontal cortex that maintains direct connections with the retrofacial nucleus (Kuipers et al. 2006) results in hypotension (Crippa et al. 2000). It is clear that the EMS indeed has a great impact on blood pressure and on the



**Fig. 9** Summary diagram of the motor systems controlled by the periaqueductal gray (PAG)



heart itself, completely dependent of what behavior is generated. For fight and flight, a higher blood pressure is needed (dorsal and lateral PAG); in case of fright (freezing), a lower blood pressure is generated (Bandler and Keay 1996).

### **Breathing**

Breathing is the motor system that inhales air from the surrounding of the individual to the lungs and vice versa in order to get access to oxygen and to get rid of the carbon dioxide. In order to inhale the air, we need a muscle that enlarges the intrathoracic space so that the lower pressure produces an airflow into the thorax. This action is called inspiration. Oxygen is taken up from this air by the lungs, and carbon dioxide is released. The most important muscle, contraction of which decreases intrathoracic pressure, is the diaphragm, which is innervated by motoneurons in the phrenic nucleus located in humans at the C3–C5 level of the cervical cord (Routal and Pal 1999). Other muscles involved in intrathoracic cavity pressure are the external intercostal muscles located between the ribs. For expiration during quiet breathing, called eupnea, no muscle activation is necessary to let the air leave the thorax, because the forces of gravity are sufficient. However, for forced expiration during strong efforts as fighting or sports, gravity is not enough, because the intrathoracic pressure has to be actively increased, which is taken care of by increasing the intra-abdominal pressure. For such an increase, contraction of the abdominal muscles, as well as of the costal diaphragm and pelvic floor muscles, is required.

There is one specific premotor interneuronal cell group in the central nervous system that has specific access to all the motoneurons of the pharynx, larynx, diaphragm, external and internal intercostal, and abdominal and pelvic floor muscles. It is the so-called nucleus retroambiguus (NRA) (Holstege 1989; Subramanian and Holstege 2009). The NRA is located ventrolaterally in the most caudal part of the medulla, caudal to the obex. The obex is the level of the transition between the fourth ventricle and the central canal that continues throughout the length of the spinal cord. The reason that these premotor interneurons are located in the caudal medulla is that at this level, information related to intrathoracic and intra-abdominal pressure enters the central nervous system through the vagal nerve. Since the NRA is the only group of neurons that specifically projects to all the motoneurons that control intra-abdominal pressure (Holstege and Kuypers 1982), the NRA is used as a tool for those regions in the CNS that control abdominal pressure. Breathing, and especially forced expiration, is an example, during which the NRA is used to acquire the extra oxygen necessary for running or for other heavy physical efforts. It is interesting that EMS structures, such as the amygdala, BNST, the lateral or other parts of the hypothalamus, preoptic area, and the orbitofrontal, which have strong access to the medulla, do not have access to the NRA (Holstege 1991; Kuipers et al. 2006). The PAG is the only suprabulbar structure that has direct contact with the

NRA (Holstege 1989), and it uses this pathway to achieve those specific motor outputs that involve intra-abdominal pressure changes.

### **Vocalization**

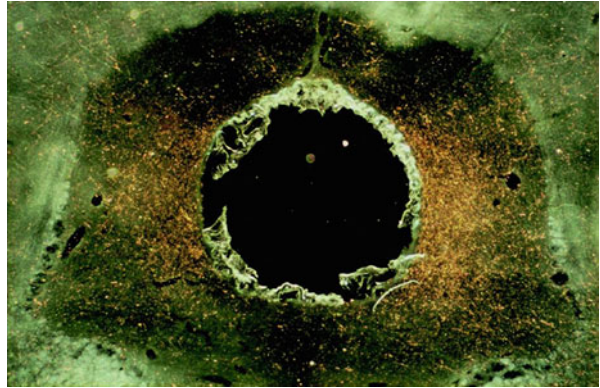
Vocalization is an example of a motor output system that involves changes in intra-abdominal and intrathoracic pressure. It explains why in animals, including monkeys, the PAG is crucial for the production of sound (vocalization). A lesion of the PAG in these animals resulted in complete mutism (Adametz and O'Leary 1959), i.e., the animals are no longer able to communicate via sound production. Stimulation in the PAG resulted in vocalization. The PAG projection to the NRA is the basis of sound production because via the NRA, the PAG has access to the motoneurons that innervate the muscles that drive air through the larynx, necessary for the vocal cords to produce sound. Animals are also able to produce different sounds, for which the PAG but also the amygdala, BNST, lateral hypothalamus, and medial orbitofrontal cortex have access to premotor interneurons in the lateral medulla that in turn control the motoneurons of the muscles that are able to modify the sound, such as pharynx, tongue, and mouth (Fig. 7, left).

In humans, the sound production is basically the same, although that is not known to most neuroscientists that study speech. Lesions in the PAG in humans, not leading to death, are rare, but three cases have been published in which PAG lesions led to mutism (Esposito et al. 1999). However, speech in humans is a combination of sound production and its modification. This modification of the sound produces words and sentences, and in order to produce these, the voluntary or somatic motor system is needed because of its great amount of memory (see paragraph on speech of the somatic motor system).

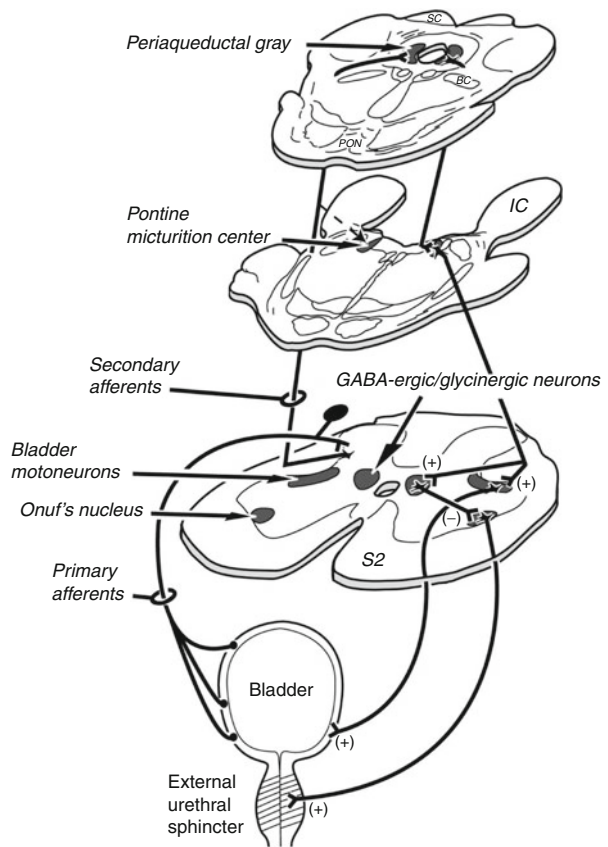
### **Micturition, Parturition, and Defecation**

One of the motor systems that belong to the lateral component of the EMS is the system that controls micturition and parturition. Also for this system, the PAG plays a crucial role. First of all, it receives all the information concerning the level of bladder filling from a cell group called Gert's nucleus (GN) in the sacral cord (Holstege 2010). GN receives, via A- $\delta$  fibers from the bladder, precise information concerning the amount of bladder filling, but it also receives A- $\delta$  fibers from the uterus (Kawatani et al. 1990) and the rectum, so that GN cells are also aware of the pressures in these two organs. GN, in turn, relays this information to the central part of the PAG (Fig. 10) but not to higher centers in the brain. The PAG, in turn, has a strong connection with the so-called pontine pelvic organ stimulating center (PPOSC). Until now, this cell group has been called pontine micturition center because of its strong control over micturition. Stimulation in the PPOSC has been shown to elicit micturition by exciting the parasympathetic preganglionic motoneurons innervating the bladder as well as, via the inhibitory GABAergic and glycinergic premotor interneurons medial to the preganglionic motoneurons, relaxation of the external urethral muscle (Holstege 2010) (Fig. 11). However, the PPOSC

**Fig. 10** Photograph of the periaqueductal gray after injecting WGA-HRP in the sacral cord. Note the strong projection to the central parts of the PAG especially contralaterally (*left side*). This projection is specifically from the sacral cord. Similar projections from other parts of the spinal cord to the PAG do not exist



**Fig. 11** Schematic drawing of the afferents and efferents as well as the ascending and descending systems involved in bladder control. Note that the same system controls uterus, distal colon, and rectum. *BC* brachium conjunctivum, *IC* inferior colliculus, *PON* pontine nuclei, *SC* superior colliculus

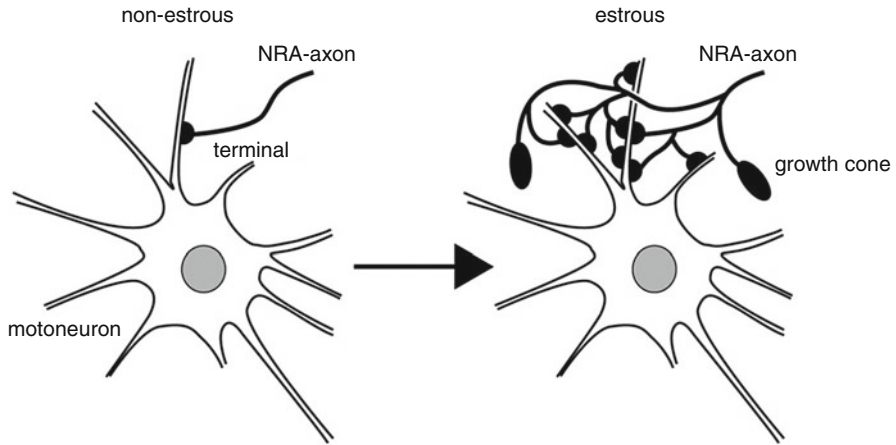


does not only project to the bladder parasympathetic motoneurons but also to those innervating uterus and rectum. Studies on stimulating the PPOSC have only examined the bladder and external urethral sphincter and not at the same time the uterus and rectum, so that the physiological effects of the PPOSC on these organs are not known. Based on the anatomical substrates, we predict that the PPOSC control of the uterus and rectum is as strong as that on the bladder. Further support for this idea comes from the finding of Holstege et al. (1986) that stimulating the PPOSC not only inhibits the external urethral sphincter but the complete pelvic floor, i.e., also the external anal sphincter and the muscles at the exit of the vagina in females. Another argument in favor of the PPOSC not only controlling micturition is that in case of patients suffering from complete transection of the spinal cord, not only micturition is in great jeopardy but also parturition, which often leads to great problems. It shows that the spinal cord plays an important role in parturition, and we predict that especially the damage of the PPOSC fibers to the sacral cord causes this problem. Transection of the spinal cord in patients also resulted in uncontrollable reflex defecation, and the persistence of external anal sphincter contraction during straining impaired fecal expulsion (Sun et al. 1995). These observations are in agreement with our concept that the PPOSC not only controls micturition but also parturition and defecation.

The reason for such a long spinal cord-PAG-PPOSC-spinal cord reflex system is that the emotional brain needs control of when to micturate, parturate, or defecate. The reason is that during these activities, the individual is not able to defend itself in case of danger, which makes it very important to verify that the environmental conditions allow these activities to take place. All structures involved in determining the presence of danger, such as amygdala, BNST, and hypothalamus, but in humans also the insula and orbitofrontal cortex, have strong access to the PAG, so that they can decide whether or not micturition, parturition, or defecation can take place. Regarding micturition and defecation, humans are usually aware of this, but since it also concerns parturition, it is of importance to take care that women in parturition find themselves in a secure and relaxed situation. If not, the brain might not give permission to the PAG to let parturition take place.

### **Sexual Activity**

In cats, it has been demonstrated that the NRA has also direct access to a specific group of motoneurons in the lumbosacral cord that induce movements that together produce the posture necessary for sexual activity (Vanderhorst and Holstege 1995). This posture differs slightly between male and female cats. In female cats, the strength of this NRA motoneuronal projection differs greatly depending on whether or not the cat is in estrous. In estrous cats, the NRA projection is almost ten times as strong as in nonestrous cats, which difference can also be obtained after giving the nonestrous cat estrogen intraperitoneally (VanderHorst and Holstege 1997a) (Fig. 12). In male cats, the pathway is always the same, stronger than in nonestrous cats but less strong than estrous cats (Vanderhorst and Holstege 1997b). It has also been shown that the PAG plays a crucial role in sexual behavior for which it uses its pathway to the NRA to produce the proper postures. Estrous cats in which the NRA

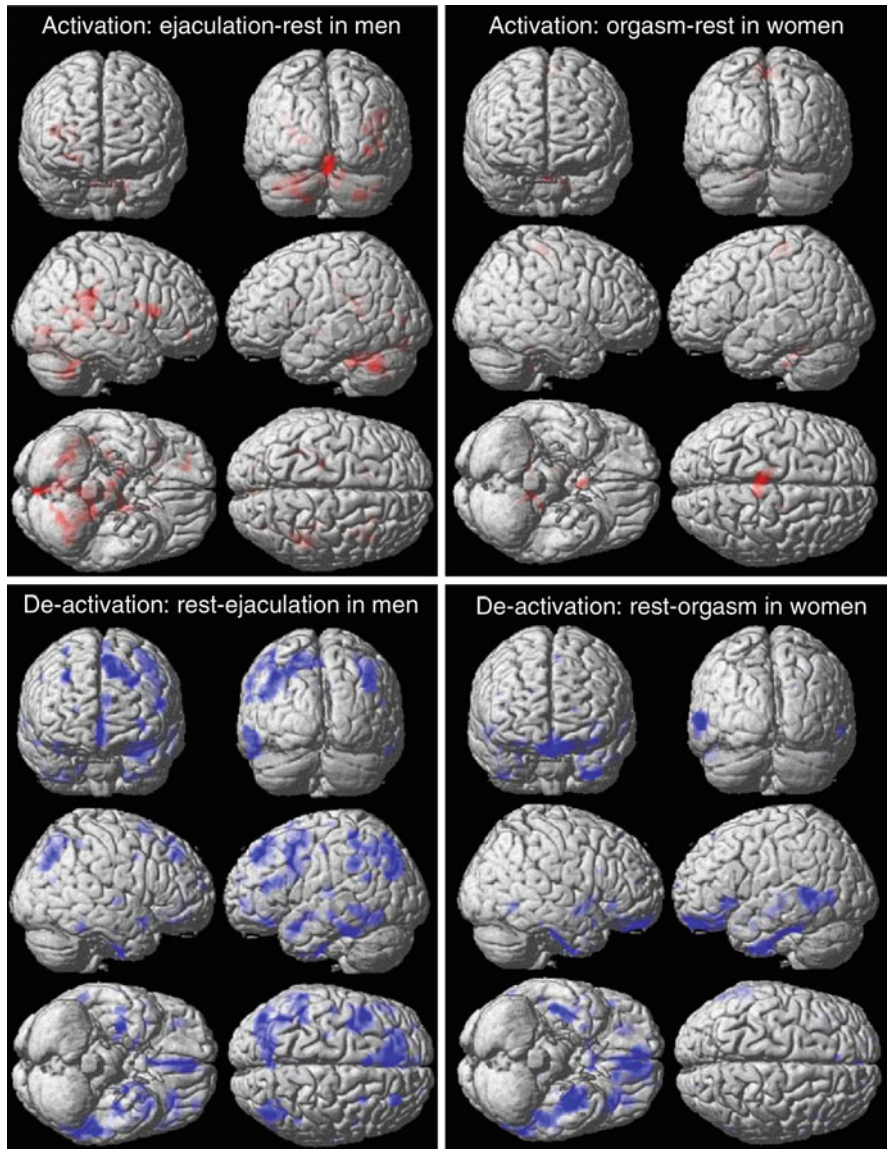


**Fig. 12** The difference between the nucleus retroambiguus (*NRA*) projection to lumbar motoneurons in the nonestrous cat (*left*) and estrous cat (*right*)

pathway to the motoneurons was interrupted were interested to have sex with a male cat but were not able to produce the right posture, despite the male cat trying this ardently (personal observations). Also this pathway is based on afferent information concerning sexual organs reaching the PAG via GN. The PAG, in turn, controls sexual activity because it can only take place when the situation is safe. The decision whether this is the case is taken by higher brain regions such as amygdala, BNST, but especially insular and orbitofrontal cortex. All these regions have strong direct access to the PAG and, thus, can inhibit sexual activity to take place if the situation is threatening.

### Sexual Intercourse in Humans

In animals as well as in humans, in situations during which the individuals are not safe and relaxed, sexual activities are difficult to perform. The reason is that the brain wants sexual activity to take place in a quiet relaxed surrounding (see above), also because the child, the result of sexual intercourse, needs to be born in a secure place. The newborn would not have a fair chance to survive in threatening conditions. For example, the menstrual cycle immediately stops in female prisoners entering concentration camps. This shows that survival of the individual is more important than survival of the species. Because of their findings in cats, Holstege et al. have also studied the brain activity of humans during sexual stimulation and orgasm (Holstege and Huynh 2011). The main result is that during successful sexual orgasm in men as well as in women, an enormous deactivation takes place on both sides of the brain but especially on the left side in the temporal lobe and prefrontal cortex (Fig. 13). Also these results indicate that the environment for sexual activities has to be nonthreatening, similar to micturition, defecation, and parturition.



**Fig. 13** Rendered brain images of the activation (*red*) and deactivation areas in men (*left*) and women (*right*) during ejaculation and orgasm. The results are from studies in which the activation was measured for 2 min in a PET scanner, while the ejaculation and orgasm only took 10–20 s. The result, therefore, is strongly diluted but still shows strong deactivation mainly on the left side of the brain

## Outlook

Both the somatic and the emotional motor system consist of a medial and a lateral component. The medial component of the somatic motor system controls the axial and proximal musculature of the body and of the position of the head on the trunk and the position of the eyes in the orbit. This component, therefore, determines the posture of the body as well as the position of the visual field. The lateral component, on the other hand, controls precise and specific movements of limbs as well as the muscles of the face, mouth, and throat. The specific limb movements produce script by means of a pen or on the keyboard of a computer. The most precise movements are made while producing speech, albeit that the sound during speech is produced by the EMS.

The medial component of the EMS is involved in a general level-setting procedure; the lateral component consists of a series of specific emotional output systems such as blood pressure control, heart rate, breathing, vocalization, vomiting (Miller 1999), parturition, micturition, and defecation, as well as aggressive behavior and freezing. All these behaviors are coordinated by the periaqueductal gray, which, in turn, receives information from the spinal cord as well as a great many instructions from higher brain levels including the prefrontal cortex and insula. These regions do not decide by themselves but receive information from the visual, auditory, and somatosensory cortex as well as from the many cortical regions representing the emotional memory of these regions.

The goal of both systems is survival of the individual and survival of the species, as already described by Benedictus de Spinoza in 1678 in Part 3 Proposition 6 of his *Ethica Ordine Geometrico Demonstrata*. We, neuroscientists, it can be seen, are discovering the mechanisms anticipated by ancient “natural philosophers.”

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