Imaging neurophysiology of human sexuality using positron emission tomography

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Mens sana in corpore sano

This thesis is dedicated to my dear parents and my dear wife Hao

CONTENTS

Chapter 1

Introduction

Aim of the thesis

Sexuality is one of the major topics of social life and one of the basic needs for survival of the species. Therefore this thesis aims at better understanding mechanisms of sexual events using brain imaging with [^{15}O]-H_2O Positron Emission Tomography (PET).

Sexuality

Sexuality in humans is defined as sexual thoughts and feelings, feeling sexually attracted to another person of different or same sex, or both sexes. Research on human sexuality consists of behavioral, social, cultural and medical studies. Sexuology is considered an interdisciplinary study of human sexuality in medical and sociological components, especially those of neurobiology, psychiatry and psychoanalysis. Using neuroimaging technologies, such as PET scanning, the study of sexuality has now made progress in understanding its physiological background.

The human sexual response cycle

The human sexual response cycle (HSRC) is a set of physiological and psychological reactions of woman or man, encompassing a complete sexual cycle studied in detail by the American sexologists Masters and Johnson. The four-stage cycle of respectively excitement, plateau, orgasm and resolution was explained in their book “Human Sexual Response” in 1966. Nowadays, a five-stage cycle is considered (Figure 1):

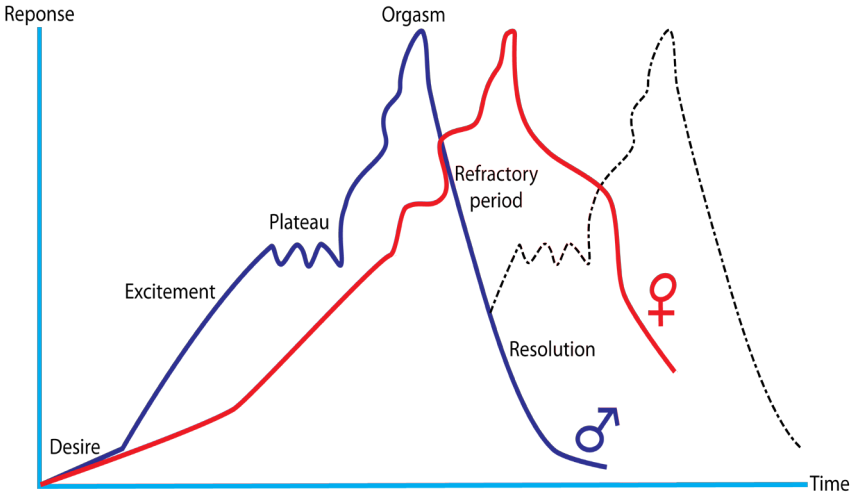

Figure 1. ***The human sexual response cycle***

1.Sexual desire

2.Excitement or sexual arousal due to sexual stimuli.

3.A plateau, characterized by an almost constant level of excitement.

4.Orgasm, as a specific motor activity at the end of the plateau, usually associated with involuntary muscle contractions of the perineum, leading to ejaculation in men and contraction of vaginal muscles and pelvic floor in women.

5.The refractory period, part of a recovery phase shortly after orgasm, during which it is physiologically impossible for an individual to have additional orgasm(s). Usually, the refractory period is longer in man than in women.

Orgasm

Orgasm is a state of extreme ecstasy during the sexual response cycle, experienced by both males and females reaching climax and resulting in rhythmic muscular contractions in the pelvic region, faster heart beat, stronger breathing and sometimes vocalizations. Called “la petite morte” in French or similarly “the little death” in English, this metaphor tries to grasp the phenomenon of orgasm. The word “orgasm” is derived from the Greek word ‘’οργασμός’’ (orgasmos), which means ‘’organ to mature or swell’’. In males, orgasm usually occurs with ejaculation. In women orgasm is usually expressed by 5-15 pelvic muscle spasms. In this thesis, the word “orgasm” is used for women and the word “ejaculation” is used for men, as ejaculation always occurred during orgasm in the men studied.

Orgasm is controlled by the central nervous system, not only involving the parasympathetic and sympathetic systems, but also regulated by hormones such as oxytocin and prolactin, released by the pituitary gland (see chapter 4 of this thesis) (Figure 2).

What is the role of orgasm? This question is still the topic of controversy, but many studies suggest that women reach orgasm during ovulation more easily, resulting in increased fertility. During orgasm the uterus expands, increasing the chance that sperm reaches an ovum. The role of orgasm increasing fertility will be discussed further in chapter 6 of this thesis.

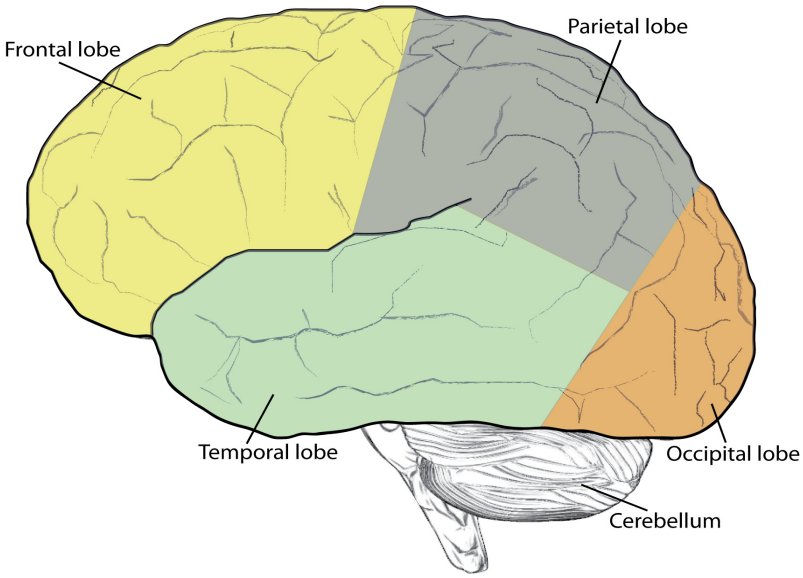

Figure 2a. ***Lobes of the brain and cerebellum***

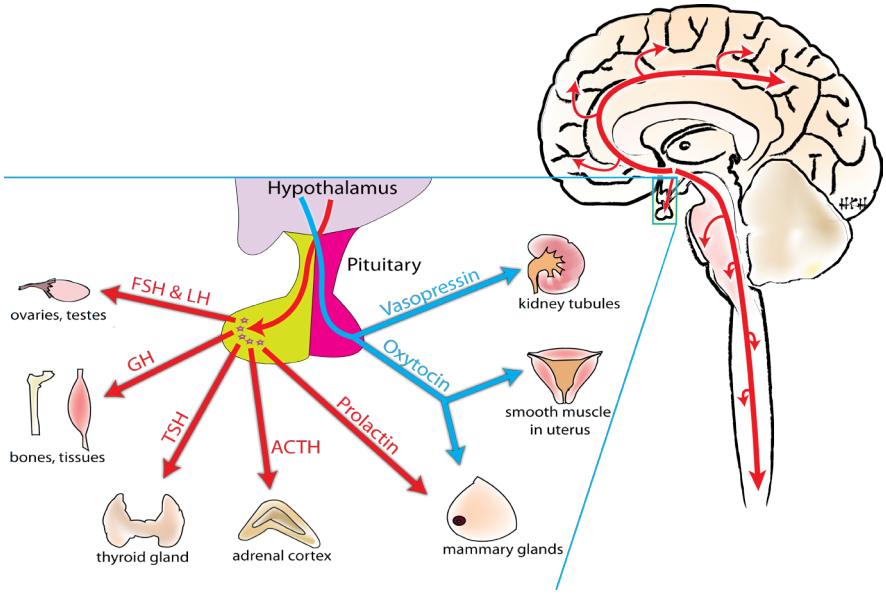

Figure 2b. ***Overview of the hypothalamic projections to the cortex cerebri, brainstem and spinal cord (red arrows) as well as to the pituitary.*** *The anterior part of the pituitary produces Follicle Stimulating Hormones (FSH), Luteinizing Hormone (LH), Growth Hormone (GH), Thyroid Stimulating Hormone (TSH), Adrenocorticotropic Hormone (ACTH) and Prolactin. The posterior pituitary releases oxytocin and vasopressin into the bloodstream.*

1 Nuclear Medicine

Nuclear Medicine is a medical specialty that utilizes radioactive substances for the diagnosis and treatment of disease (Figure 3). Nuclear medicine differs from most other medical imaging techniques (e.g. CT, MRI, Ultrasound) in that it obtains physiological rather than anatomical images.

In nuclear medicine practice, radionuclides are combined with existing pharmaceutical compounds to constitute radiopharmaceuticals. These radiopharmaceuticals, once properly introduced into the patient's body by injection, ingestion or inhalation, distribute through the body. Depending on the characteristics of the selected radiopharmaceutical their accumulation reflects a specific physiological process (e.g. perfusion or metabolism) or condition (e.g. receptor density). As such, they can localize specific organs or cellular receptors to image the extent of disease processes, based on the cellular function and physiology rather than physical changes in the tissue anatomy. Since physiological changes often precede anatomical changes they can identify medical problems at an earlier stage than other diagnostic tests.

Nuclear medicine is now employed to study virtually all systems of the human body with applications in many medical specialties, including neurology, cardiology, oncology, endocrinology, nephrology and various surgical disciplines in both human and animal research.

Imaging with gamma cameras

The main imaging modality in nuclear medicine is the gamma camera. It generally consists of two detector heads which allow two simultaneous views of the radioactivity distribution in the patient's body. Each view is a projection, which is created by a collimator which is positioned directly in front of the detector. Normally this is a parallel hole detector giving a parallel, planar projection. However, diverging or zooming collimators can also be used which results in an enlarged projection on the detector. By combining multiple views from different directions a three-dimensional reconstruction of the activity distribution can be obtained. The image quality of gamma systems is dominated by the characteristics of the collimator, which limit both the resolution and sensitivity. This limitation is overcome by PET systems, which do not require a collimator.

Principles of Positron Emission Tomography scanning

PET-scanning is based on the decay of positron emitting isotopes. The positron is the anti-particle of the electron with identical properties except for its charge, which is positive. The positron slows down in a few millimeters by its interaction with tissue. It will then annihilate with an electron, which

results in the production of 2 annihilation photons. From the conservation of energy it follows that each photon has an energy of 511 keV while the conservation of momentum requires the two photons to travel in a straight line in opposite directions. By creating a cylindrical detector both photons can be detected simultaneously i.e. coincidence detection (Figure 4).

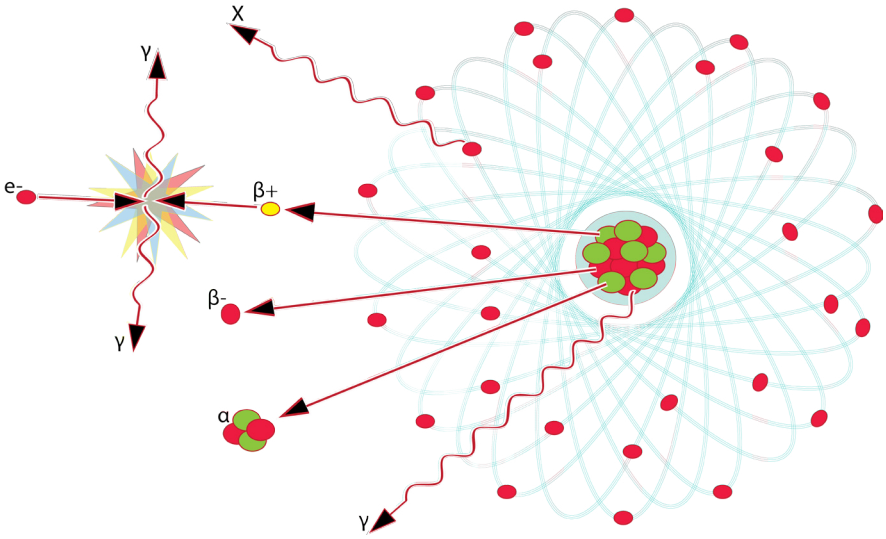

Figure 3. ***Different types of radioactive radiations used in nuclear medicine*** *(Gamma, Alpha, Positron, Beta-minus and X-rays)*

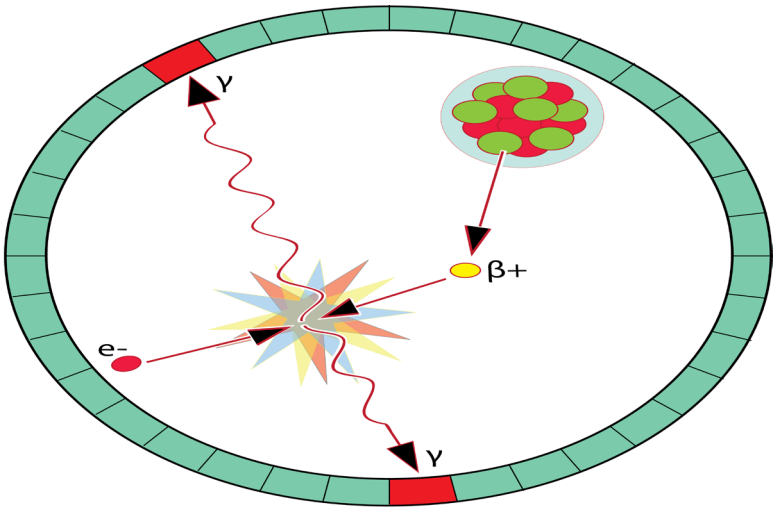

Figure 4. ***Basic principle of positron emission tomography:*** *a coincidence is counted when two detectors in two opposed directions simultaneously detect two photons from an annihilations of a positron and an electron.*

Since the photons travel on a straight line, the connecting line between the two detectors (the line of response) represents the projection of the radioactive decay. This is sometimes referred to as electronic collimation. Thus in PET a collimator is not required, immediately improving the sensitivity and resolution of PET in respect to gamma systems.

An additional advantage is in the characteristics of the used isotopes. The most interesting positron emitting isotopes are ^{11}C, ^{13}N, ^{15}O and ^{18}F. In particular ^{11}C is interesting as it allows the synthesis of compounds, which will be bio-chemical identical to native compounds provided that the isotope is at the position of a (non-radioactive) ^{12}C atom. The same goes for ^{13}N and ^{15}O. However, ^{18}F is usually introduced in the position of a hydrogen atom and will thus change the properties of the molecules. Chemically speaking, the main disadvantage of ^{11}C is its short half-life of only 20 min, which greatly limits the production. This is even more the case for ^{13}N and ^{15}O with half-lifes of only 10 and 2 min respectively whereas the main advantage of ^{18}F is its relatively long half-life of 2 hours. However, even ^{15}O can be used as for example in $[^{15}O]$-H_2O (oxygen-15 labelled water).

Labeled water is very interesting as its distribution reflects tissue perfusion. This is interesting for neuroscience applications, as it is well known that changes in regional neural activity result in changes in regional tissue perfusion. Even better, this brain overshoots i.e. the change in perfusion is larger than is required to maintain homeostasis. This technique is used in this thesis to investigate the effect of different external stimuli on the regional brain perfusion i.e. the regional brain activity. Since ^{15}O has a very short half-life, up to 12 repeated measurements are possible with about 10 min intervals.

Different techniques are available for brain activation studies. The majority of studies is now performed with functional MRI (fMRI). As compared to PET, fMRI has a main advantage that it does not rely on the use of ionizing radiation. However, the sensitivity of fMRI for a single activation is quite low and only through the averaging of many responses can an activation be determined. In most cases this is not a problem since most activations are very short enabling multiple repetitions. However, when only a limited number of activations is possible as in our studies, PET is a better option since it has a higher sensitivity per activation and only allows a limited number of activations anyway (remember that the scan interval is about 10 min). An additional problem with fMRI is that it is very sensitive to motion. Generally, motion correction techniques are adequate to handle this problem but in the case of sexual arousal studies the expected head motion is probably too large. Finally, fMRI is particularly suited for studies of the brain cortex but less so for deeper brain structures such as the brainstem.

Data analysis

Statistical Parametric Mapping (SPM) process

SPM is a software package running in Matlab to construct and assess spatially extended statistical processes used to test hypotheses about functional imaging data for the analysis of brain imaging data sequences of fMRI, PET, SPECT, EEG and MEG.

Therefore a number of steps are required. Here we describe the general processing relevant for the analysis of PET data (Figure 5). In individual studies additional (pre-)processing may be employed. First the different scans of subject are realigned to compensate for small motions of the brain between the different activation scans. Once this is completed we need to transform the scans of the different subjects to a common reference frame so that the data from each brain area can be compared across subjects. Therefore a non-linear spatial normalization is employed which warps the individual brains to the so-called Montreal Neurological Institute (MNI) template. Since PET has a relatively low resolution and the PET images used also have limited anatomical references (after all, PET is a functional technique not a morphological one), the spatial normalization will be limited in its accuracy a small remaining registration errors are to be expected.

Therefore, an additional spatial smoothing is applied which should ‘smear out’ the activations and increase the likelihood of overlapping activations between studies. An additional advantage of this filter is that it increases the signal-to-noise ratio of the data provided that the activations are not too small.

After these processing steps the statistical modeling itself can commence. Statistical testing is performed for each pixel separately by a t-test. Both uncorrected and corrected for multiple comparison p-values are given together with the coordinates of peaks in the t-maps. These coordinates help with the localization of the brain structures, which show activations or deactivations. The data model is represented graphically showing the groups, subjections and conditions as well as the global cerebral blood flow value which is used to scale the individual measurements.

For the data presented in chapter 4, an additional motion correction was applied (Figure 2 in Chapter 4) to previously published data on female orgasm and male ejaculation.

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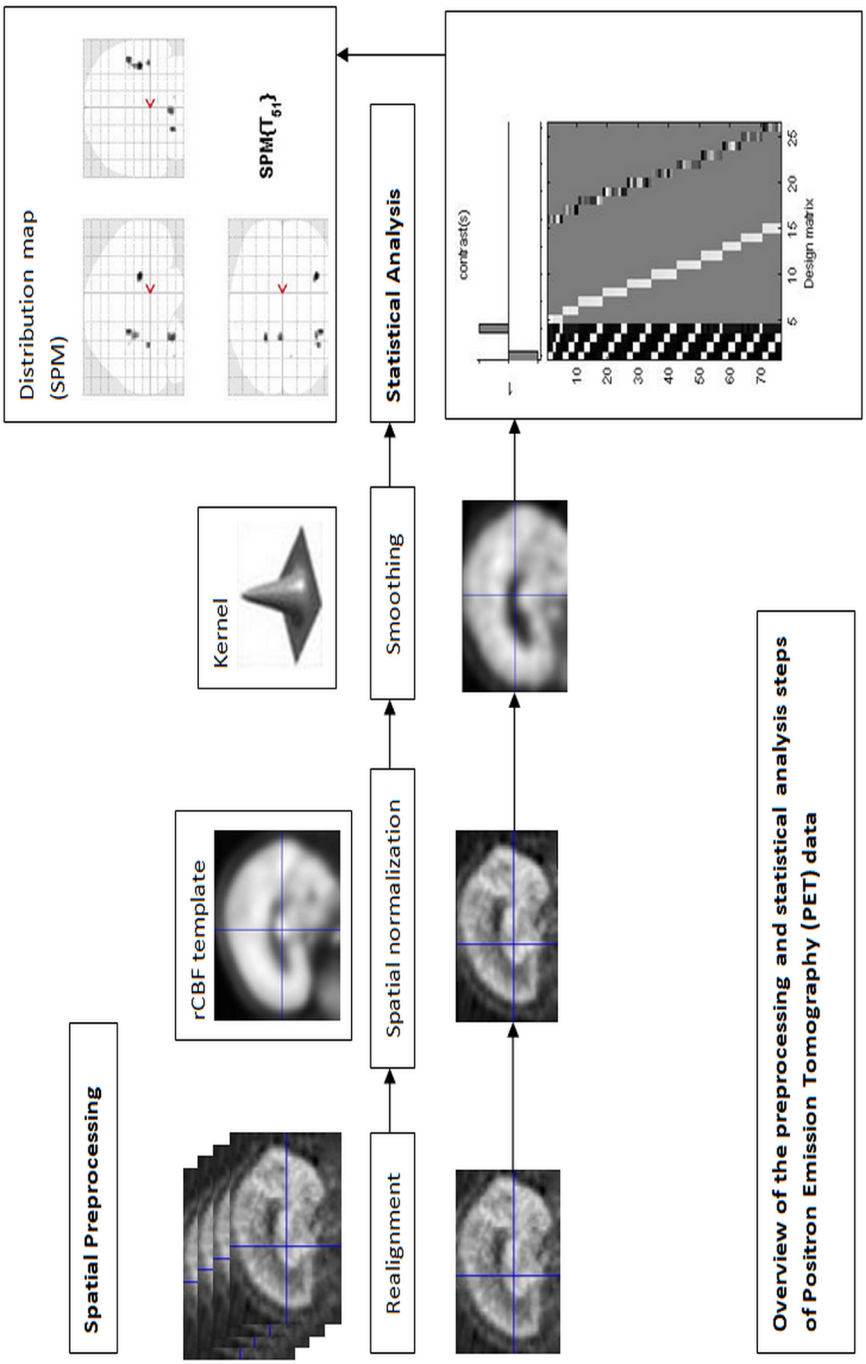

Figure 5. ***Overview of the preprocessing and statistical analysis steps in PET data process.***

Chapter 2

Brain circuits for mating behavior in cats and brain activations and de-activations during sexual stimulation and ejaculation and orgasm in humans

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Hormones and Behavior 2011 May;59(5):702-7

Abstract

In cats, there exists a descending system that controls the posture necessary for mating behavior. A key role is played by themesencephalic periaqueductal gray (PAG), whichmaintains strong specific projections to the nucleus retroambiguus located laterally in the most caudal medulla. The NRA, in turn, has direct access to motoneurons in the lumbosacral cord that produce the mating posture. This pathway is slightly different in males and females, but in females its strength fluctuates strongly depending on whether or not the cat is in heat. This way the PAG determines whether or notmating can take place. Via the PAGmany other regions in the limbic systemaswell as in the prefrontal cortex and insula can influence mating behavior.

In humans, the brain also controls responses to sexual stimulation as well as ejaculation in men and orgasm in women. Neuroimaging techniques show activations and de-activations but are not able to verifywhether the PAG has a similar effect as in cats. PET-scanning results revealed that there is activation in the upper brainstem and cerebellum, as well as insula in men and in the somatomotor and somatosensory cortex in women. During sexualstimulation, but especially during ejaculation and orgasmtherewas strong de-activation mainly on the left side in the temporal lobe and ventral prefrontal cortex. These neuroimaging results showthe importance of lowering the level of alertness regarding your immediate environment (left hemisphere) to have proper sexual behavior.

How is it that a neuroscientist becomes interested in the way the brain controls sexual behavior, especially a neuroscientist who has studied brainstem and spinal cord connections in animals? The reason is that basic neuroanatomical tracing techniques revealed connections that appeared to constitute the hardware for the sexual posture in male and female cats (VanderHorst and Holstege, 1995; 1998). This finding inspired the idea to find out, using neuroimaging techniques, whether we could also detect a similar system in humans. The results show the higher brain activations and de-activation in humans during sexual behavior, which could not be studied in cats. However, the question, whether the hardware system in cats is also present in humans still remains to be resolved.

The sexual posture system in cats

A central role in producing the sexual posture is played by the so-called nucleus retroambiguus (NRA). It plays an important role in the so-called lateral component of the emotional motor system (Figure 1; Holstege, 1992).

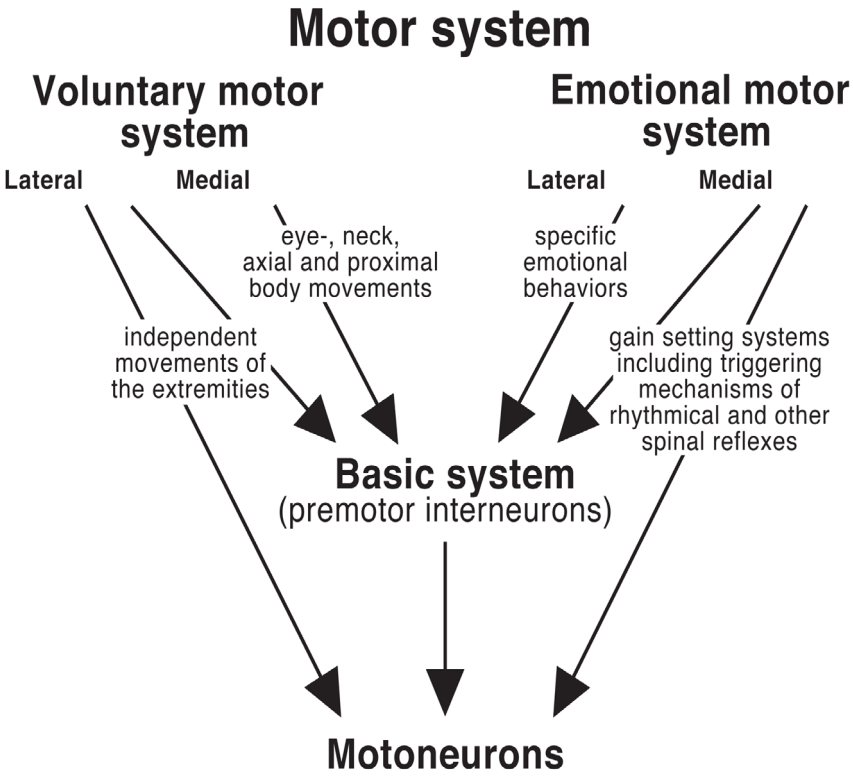

Figure 1. ***Schematic scheme of the two components of the motor system.***

The NRA is a relatively small group of cells located ventrolaterally in the most caudal portion of the brainstem. Merrill (1970) was the first to demonstrate that this cell group was strongly involved in respiration control. Indeed the nucleus retroambiguus projects to the motoneurons of those muscles that control the intra-thoracic and intra-abdominal pressure. These muscles are the diaphragm, external and internal intercostal, abdominal and pelvic floor muscles (Holstege and Kuypers, 1982, Holstege and Tan 1987; Figure 2) and even the very thin cutaneous trunci muscle (Boers et al. 2006). Later studies (Subramanian and Holstege, 2009) showed that this projection is of crucial importance for all systems, that involve changes in abdominal pressure, not only respiration, but also vomiting, vocalization, coughing, and parturition.

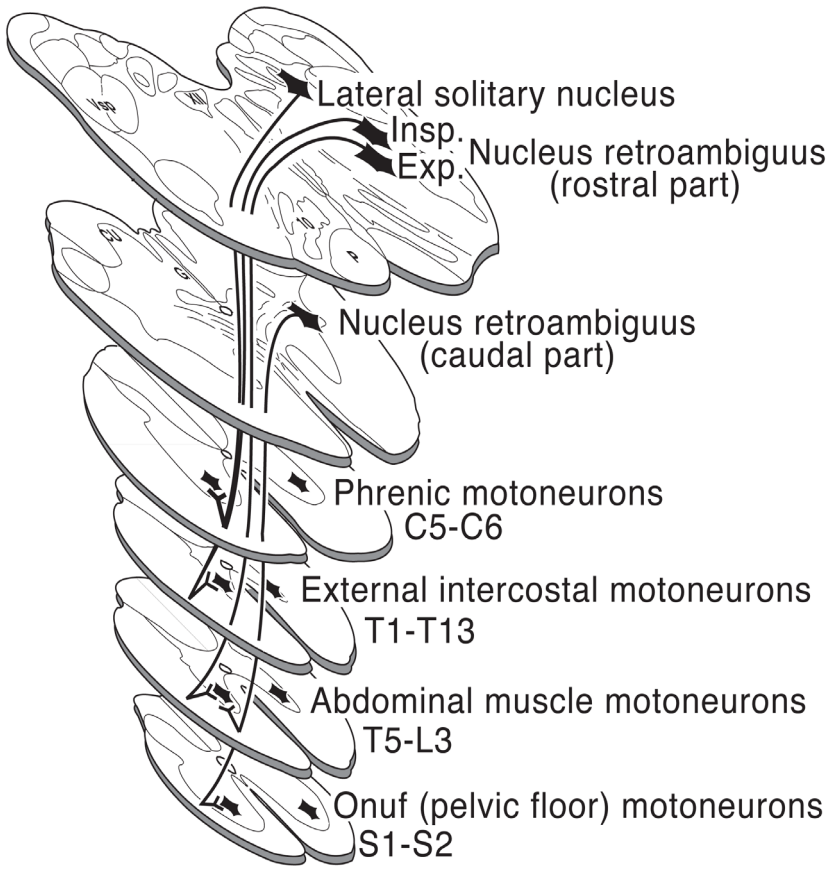

Figure 2. ***Schematic scheme of the pathways from the solitary nucleus and the nucleus retroambiguus to the spinal cord.*** *The nucleus retroambiguus is the only nucleus that contains neurons that have specific access to all motoneurons involved in abdominal pressure control.*

Already in 1979 in cat we discovered an extra but rather weak projection from the NRA. NRA fibers appeared to descend throughout the length of the spinal cord to terminate on motoneurons of the upper limbs and caudal trunk. Combining the function of these motoneuronal cell groups suggested a certain posture that fitted the posture of female cats during sexual behavior (Figure 3). They display a very specific posture, necessary for male cats to penetrate during sexual intercourse. If this pathway indeed was the basis of this behavior, it was not clear why the projection was so weak. Later studies showed that the impact of this pathway on motoneurons differed strongly, depending on whether or not the cat was in estrous. Injecting estrogen in ovariectomized female cats also resulted in a much stronger NRA-lumbosacral motoneuronal pathway (VanderHorst and Holstege, 1997a). A subsequent electron microscopic study demonstrated that estrogen is able to increase the number of terminals of one particular NRA fiber terminating on lower leg motoneurons involved in the copulation posture (Figure 4). In a male study the NRA pathway to the lower limb motoneurons was slightly different from the female projection system, and was stronger than in the non-estrus female cats, but weaker than in female cats in estrous (VanderHorst and Holstege, 1997b).

These results demonstrate that in cats a descending pathway exists from the NRA to motoneurons of the lower limb and trunk that produce the posture for males and females necessary to copulate. A small lesion in the spinal cord, interrupting this pathway on one side, produced female cats that were only able to produce the proper posture on the non-lesioned side, but not on the lesioned side. It was sufficient to make it impossible for healthy male cats to copulate, although the female cat was in estrous and willing.

Not all neurons of the NRA project to the lumbar sexual posture motoneurons, only those located in the more caudal parts of this nucleus. Neurons in more rostral parts of the NRA project to laryngeal and pharyngeal motoneurons in the nucleus ambiguus, and to the diaphragm and intercostal motoneurons. The NRA neurons that project to abdominal muscle motoneurons are located caudal to those and the NRA neurons in the most caudal NRA project to the sexual posture motoneurons in the lumbosacral cord and to the pelvic floor motoneurons in the nucleus of Onuf (Figure 2).

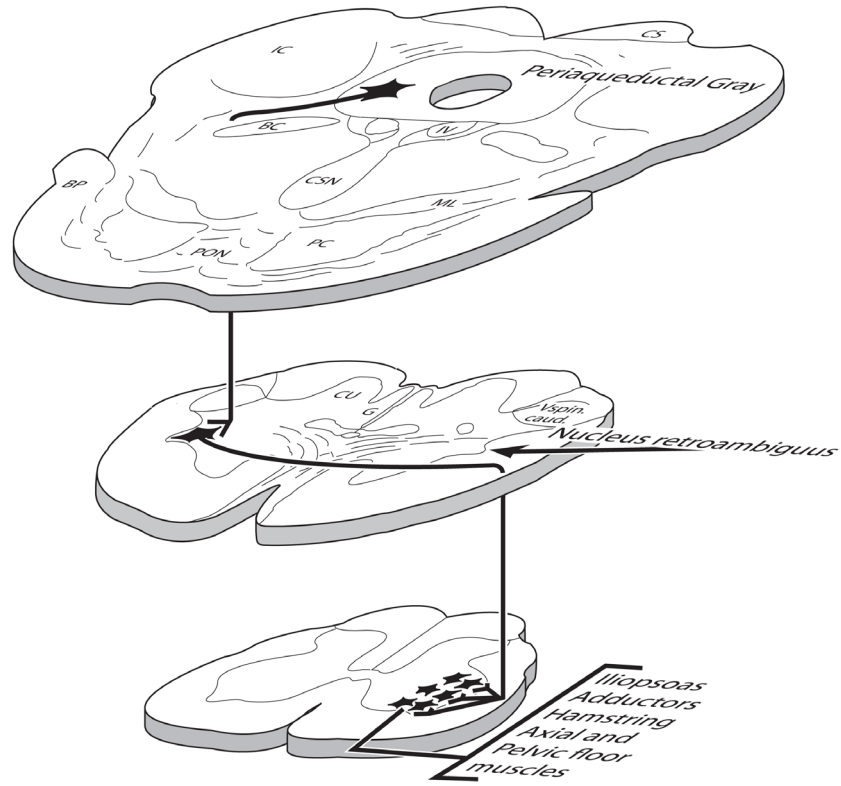

Figure 3. ***Schematic overview of the projections from the periaqueductal gray via the nucleus retroambiguus to the motoneurons that control the mating posture in female cats.***

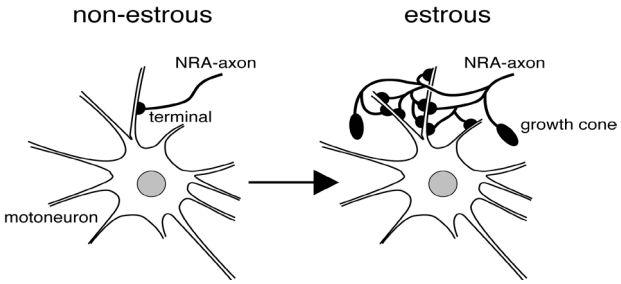

Figure 4. ***Schematic description of the termination of an axon of a neuron of the nucleus retroambiguus terminating on a motoneuron in the lumbosacral cord.*** *In non-estrous cats this projection pattern is limited, but in case of estrous cats, as well as in ovariectomized female cats injected with estrogen, this terminal develops growth-cones which produce the energy to produce almost ten times as many terminals on the same motoneurons as in non-estrous cats. It also explains why the mating behavior in cats is so different from non-estrous cats.*

The next question is what part of the central nervous system controls the NRA. Several limbic system structures as the central nucleus of the amygdala, lateral bed nucleus of the stria terminalis, and lateral hypothalamus, as well as the orbitofrontal cortex have direct access to the pontine and medullary lateral tegmental field in the caudal brainstem. Although the NRA takes part in this lateral tegmental field, it does not receive afferents from the structures mentioned above. On the other hand, the NRA receives very strong projections from the mesencephalic periaqueductal gray (PAG; Figure 5). The PAG, therefore, has direct control over the height of abdominal pressure, since the NRA is the only cell group that has direct access to all motoneurons of the muscles controlling abdominal pressure. Examples in which abdominal pressure plays a role are vocalization, vomiting, non-eupneic respiration, parturition, as well as sexual activities. In fact, the PAG, via its projections to the Pontine Pelvic Organ Stimulating Center (PPOSC), also controls bladder and intra-uterine pressure, i.e. micturition and uterine contractions during parturition. Since the PAG, in turn, receives precise information regarding intra-abdominal, bladder and intra-uterine pressure from Gert's nucleus in the sacral cord, as well as from the prefrontal and insular cortex, amygdala, bed nucleus of the stria terminalis and hypothalamus, it plays a central role in how the emotional brain controls basic motor activities as respiration, vocalization, vomiting, micturition, and parturition. The involvement of the emotional brain in sexual behavior in humans became clear studying the cerebral (de-) activation of the human brain during sexual stimulation and orgasm.

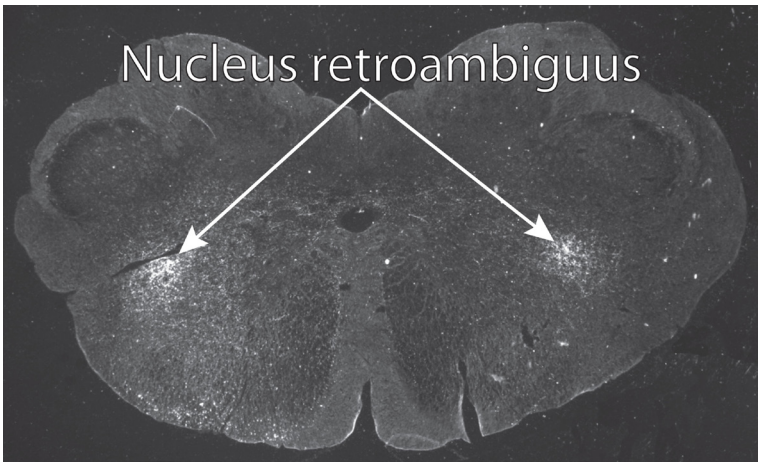

Figure 5. ***Darkfield photomicrograph of a section of the caudal medulla in a cat in which tritiated leucine was injected in the ventrolateral periaqueductal gray (PAG).*** *Note the specific projection to the nucleus retroambiguus. Indicating the strong control of the PAG on abdominal pressure and mating behavior.*

Neuroimaging of sexual behavior in men and women

Our findings in the cat triggered our interest in how sexual behavior is organized in humans. The study was done in male and female heterosexual volunteers. Since there were no earlier studies that had investigated the brain activation and de-activation during sexual stimulation, it was not clear whether such a study on sexual stimulation and/or orgasm in a PET-scanner was possible. It appeared one of the very few studies that were easier to perform than anticipated. The question how to find volunteers that would be interested to perform sexual behavior lying with their head still in the scanner was easily solved. All kinds of people, students, businessmen, secretaries etc. from The Netherlands and Flanders, the Dutch speaking part of Belgium, were happy to participate. The question was whether they would be able to keep their heads still during sexual stimulation and orgasm. The male or female volunteers were not allowed to perform the stimulation him- or herself, because that would lead to activation of brain regions as cortical hand- or arm regions, not specifically involved in sexual behavior. We solved this problem by asking the partners of the volunteers to perform the stimulation. Since the volunteers were heterosexual, the male volunteers by their female partner, and the female volunteers by their male partner. The volunteers were told what was expected from them, but during the scanning period itself, when they were lying with their heads in the scanner, they were not bothered by details as at exactly which moment they had to perform a certain task. This prevented the volunteers to perform brain activities that had no connection with the basic task, undergoing sexual stimulation and ejaculation or orgasm. The partners, on the other hand, were continuously told what was expected at what time from the volunteer. They were precisely aware of the situation and knew eight minutes ahead which performance had to take place. This way it was possible to have ejaculations or orgasms in the time period the scanner was active, i.e. between 20 and 60 seconds after administering saline with $[^{15}O]$-H_2O intravenously through the right arm. In about 50% of the cases we had successful ejaculation at the right moment; in the female volunteers this percentage was even higher.

Technical problems

For the ejaculation and orgasm tasks there was a major technical problem. The PET-scanner always measured radioactivity during exactly two minutes. Since the results show the differences between the amount of blood in the various brain regions during “rest” compared to “stimulation”, “ejaculation” or “orgasm”, all these tasks had to be performed during two minutes. However,

ejaculation and orgasm do not last two minutes but 10-20 seconds. For this reason, for our first report the timescale of this task was subdivided into 10s timeframes (Holstege et al. 2003). These timeframes were compared with the two minutes frames of rest or stimulation. In the study on female orgasm (Georgiadis et al. 2006) we compared the 60 sec. frames with 60 sec. timeframes of rest, imitation of orgasm or clitoral stimulation. In a later study (Georgiadis et al. 2007) the same results were studied, using the complete two minutes frames of the ejaculation and orgasm tasks. Since ejaculation or orgasm took place during only 10-20 seconds of the 120 sec timeframes, a strong dilution of the activation and de-activation took place compared to the theoretical situation in which ejaculation or orgasm would continue during the full 120 sec timeframe. Nevertheless, the results still show strong activated and de-activated regions.

In the present paper we again have re-analyzed the results by making corrections for head movements. For obvious reasons these head movements during tasks as stimulation, ejaculation and orgasm were stronger than in PET-studies in which it was easier for the volunteers to keep their heads still.

The men study

Activated regions

The results of the men study showed that comparing stimulation of the penis with rest activated the right posterior insula and a large region in the deep dorsal posterior temporal lobe. Comparing ejaculation with rest revealed a similar activation of the right posterior insula, but a much stronger activation of the deep dorsal posterior temporal lobe. Moreover, this comparison also revealed strong activation of the central midbrain and medial globus pallidus bilaterally. There was also strong activation in major parts of the cerebellum, including the deep cerebellar nuclei, vermis and hemispheres bilaterally (Figure 6).

De-activated regions

Comparing rest with stimulation revealed regions that became less active during stimulation, i.e. became de-activated. One of these regions was the amygdala bilaterally, although this de-activation was not found comparing rest with ejaculation. Another region that was de-activated during stimulation as well as ejaculation was the ventral part of the temporal lobe, bilaterally, but mainly on the left side. During stimulation no further de-activations were observed, but during ejaculation several de-acted regions were found in extended regions of the parietal, prefrontal, medial orbitofrontal and

temporal cortex. These de-activations were found mainly on the left side (Figure 7).

Women study

Activated regions

In women comparing clitoral stimulation with rest revealed activation in the somatosensory and somatomotor cortex, and especially the medial aspect of it. This part represents the pelvic region. Also in the comparison orgasm minus rest this same region comes up, but less strongly activated than in the stimulation minus rest comparison. In the orgasm-rest comparison activation was also found in the rostral part of the medial cerebellum, which was not found in the stimulation-rest comparison (Figure 8).

De-activated regions

Also in women the de-activated regions were much larger than the activated areas. Comparing rest with clitoral stimulation reveals that there was bilateral de-activation in the amygdala, but mainly on the left side. De-activation was also found in the most posterior parts of the temporal lobe on the left side. The same region was also de-activated comparing rest with orgasm, but extended rostrally into the ventral part of the temporal lobe and into the ventral part of the prefrontal cortex. These regions of de-activation were bilateral, but mainly on the left side (Figure 9).

Conclusion of both human studies

In both men and women the activated cortical regions were mainly on the right side, while the de-activated areas were mainly on the left side. As we already found in the women study of 2006 in this re-analysis of the results in men the total de-activated brain regions were much larger than the activated regions. However, in the mesencephalon and cerebellum we only found activation and no de-activation.

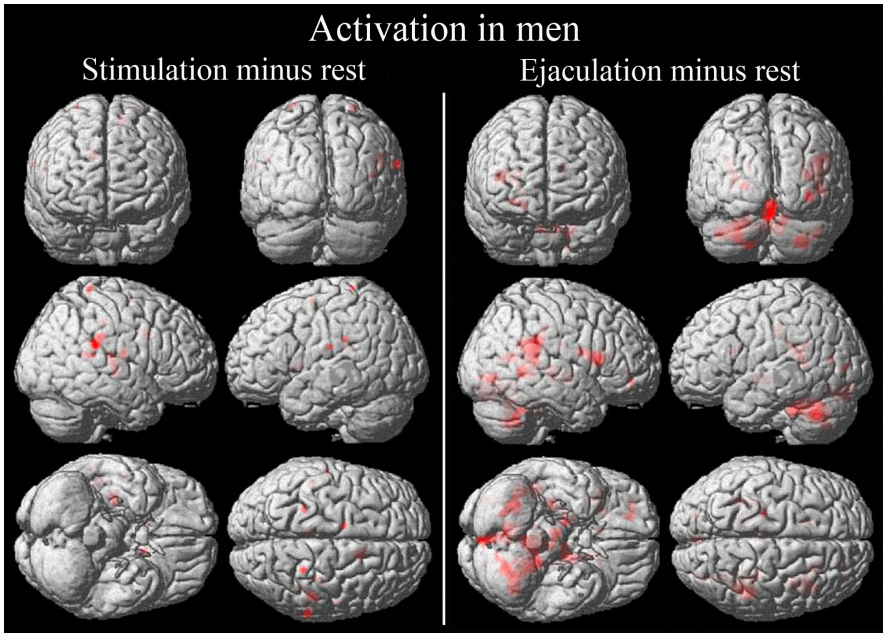

Figure 6. ***Activation patterns in men on a volume or rendered brain. On the left stimulation-rest, on the right ejaculation-rest.***

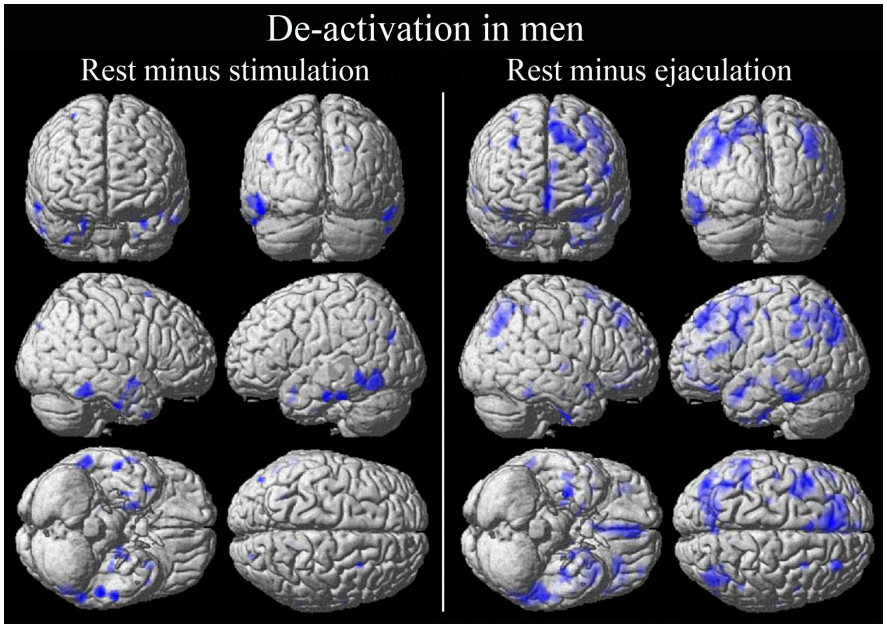

Figure 7. ***De-activation patterns in men on a volume or rendered brain. On the left rest-stimulation, on the right rest-ejaculation.*** *Note that the de-activation is mainly on the left side of the brain.*

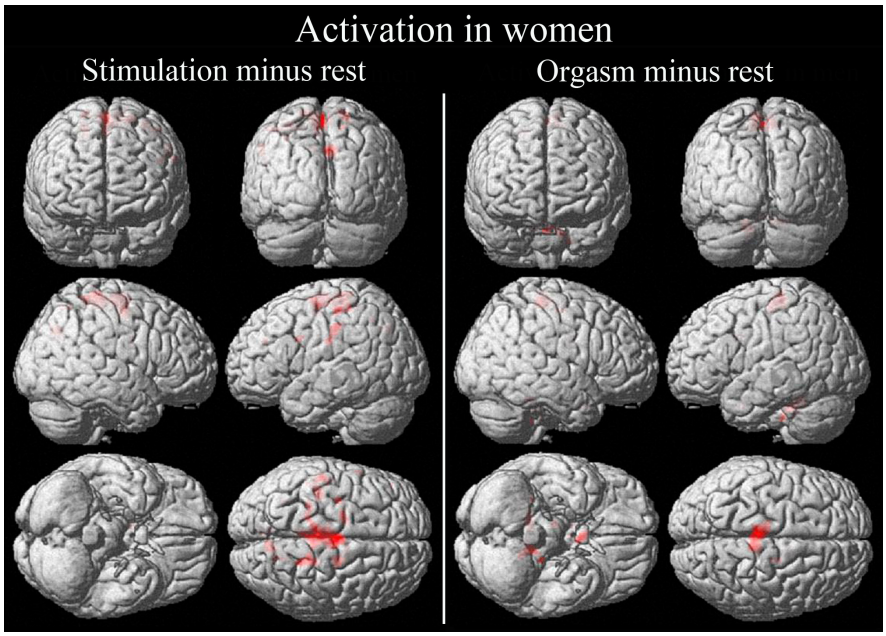

Figure 8. ***Activation patterns in women on a volume or rendered brain. On the left stimulation-rest, on the right orgasm-rest.***

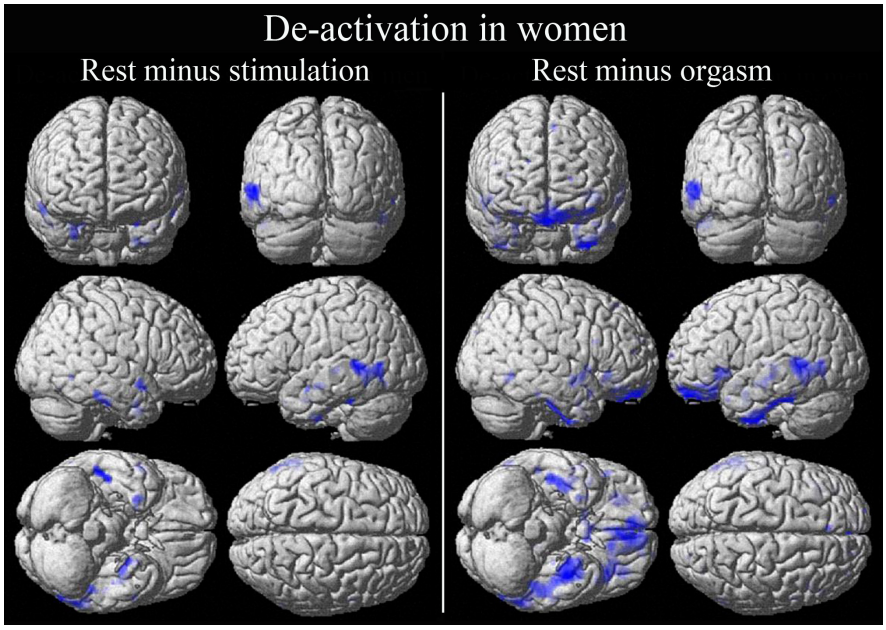

Figure 9. ***De-activation patterns in women on a volume or rendered brain. On the left rest-stimulation, on the right rest-ejaculation.*** *Note that the de-activation is mainly in the ventral parts of the temporal lob and prefrontal cortex.*

Our results demonstrate that the major effect of ejaculation and orgasm is not activation of certain regions but de-activation. These regions are all involved in emotional processing, and it is clear that emotional processing of the left brain is not considered to be important during sexual stimulation or ejaculation/orgasm. The left hemisphere is thought to be rational and processes established certain information and controls feelings. Within this framework it also processes speech and writing. The right hemisphere, on the other hand, is intuitive, spontaneous, and free with feelings. The present results show that during sexual stimulation and ejaculation and orgasm in men and women rational thinking and processing of specific information is downgraded, but the brain areas involved in spontaneous emotional processing are, albeit to a limited extent, activated.

In clinical terms these results show that high levels of alertness and fear don't go together with sexual behavior. For proper sexual behavior one has to "let it go". It might also explain the reason for hypoactive sexual desire disorder in women, which occurs so frequently (20-30% of all women; Hayes et al. 2007).

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Chapter 3

High-intensity erotic visual stimuli de-activate the primary visual cortex in women

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Abstract

Introduction. *The primary visual cortex, Brodmann's area (BA 17), plays a vital role in basic survival mechanisms in humans. In most neuro-imaging studies in which the volunteers have to watch pictures or movies the primary visual cortex is similarly activated independent of the content of the pictures or movies. However, in case the volunteers perform demanding non-visual tasks, the primary visual cortex becomes de-activated, although the amount of incoming visual sensory information is the same.* ***Aim.*** *Do low- and high-intensity erotic movies, compared to neutral movies, produce similar de-activation of the primary visual cortex?* ***Methods.*** *Brain activation/de-activation was studied by PET-scanning of the brains of 12 healthy heterosexual premenopausal women, age 18-47, who watched neutral, low- and high-intensity erotic film segments.* ***Main Outcome Measures.*** *We measured differences in regional cerebral blood flow (rCBF) in the primary visual cortex during watching neutral, low-intensity erotic, and high intensity erotic film segments.* ***Results.*** *Watching high-erotic, but not low-erotic movies, compared to neutral movies resulted in strong de-activation of the primary (BA 17) and adjoining parts of the secondary visual cortex.* ***Conclusions.*** *The strong de-activation during watching high intensity erotic film might represent compensation for the increased blood supply in the brain regions involved in sexual arousal, also because high intensity erotic movies do not require precise scanning of the visual field, because the impact is clear to the observer.*

Introduction

It is common knowledge that sex is between the ears, which means that most people realize that the brain plays a crucial role in sexual activities. The next question is how the brain processes sexual activity. One approach is to show men and women erotic movies and study brain activation and de-activation by neuro-imaging.

Almost all neuro-imaging studies, using visual information, result in many different activation patterns in the brain. The activation level of the primary visual cortex, also known as Brodmann's area (BA) 17, which plays a crucial role in receiving the visual information, remains the same, independent of the content of the visual information. However, auditory tasks signals, that require demanding judgments, resulted in de-activation of the primary visual cortex, despite in both tasks the amount of visual sensory information remained the same (Yoncheva et al., 2010). The apparent explanation for such a downgrade of the primary visual cortex is that it not only receives information from the eyes, via the lateral geniculate thalamic nucleus, but also from several regions in the temporal cortex. Examples are the secondary (V2 or BA18), tertiary (V3, BA19), quaternary (V4, BA19), and quinary (V5, BA19) visual cortices, as well as the ventral temporal lobe (BA 20) and the amygdale.

Another de-activation of the primary visual cortex was observed in studies in men watching explicit erotic movies compared to rest, despite equal visual incoming information (Miyagawa et al., 2007; Mouras et al., 2003; Tsujimura et al., 2006). However, these results were not very outspoken, which brings up the question whether sexual visual stimuli really downgrade the activation level of the primary visual cortex. Since in women no studies exist on the relationship between visual sexual stimuli and activation or de-activation of the visual cortex, we have investigated whether low-intensity erotic or high erotic movies, compared to neutral movies, produce de-activation in the primary visual cortex. A positive finding would fit with the concept that sexual behavior is considered of primary importance within brain function.

Methods

Participants

A total of 12 healthy heterosexual premenopausal women, age 18-47 were involved in this study. They were recruited by the Center for Uroneurology and the Department of Gynecology of the University Medical Center

Groningen. Prior to the volunteers' participation in the trial, they were fully informed, the procedures were explained and they signed an informed consent form, according to the Declaration of Helsinki and the regulatory and legal requirements of the European Union. The Medical Research Ethics Committee of the University Medical Center and University of Groningen has approved the study.

In order to ascertain that the volunteers did not suffer from any sexual problems, inclusion was based upon a complete medical and sexual history, including a physical examination and clinical laboratory tests. A complete assessment of the volunteers' medical and sexual (dys)function, as well as their social and psychiatric history was performed, including the Female Sexual Distress Scale-Revised, question 2 of the Sexual Interest and Desire Inventory, assessment of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and the Beck Depression Inventory-II (BDI-II) (Beck AT et al., 1996). Only those who met these criteria were invited to participate in the study.

Inclusion criteria were:
1. Premenopausal (18 years or older);
2. Hormonal contraceptive therapy during more than 3 months before the PET-scanning procedure in order to prevent differences in interest in visual sexual stimuli during the menstrual cycle;
3. Stable monogamous heterosexual relationship that was secure and communicative for at least one year prior to the screening visit;
4. BMI ≤29 kg/m²;
5. Subject is reliable and willing to give written informed consent prior to participation in the trial;
6. No primary diagnosis of any sexual disorder according to the DSM-IV-TR® criteria.

Exclusion criteria were:
1. Pharmacologic: medications known to affect sexual response, drug dependence, etc.;
2. Gynecologic: pregnancy, breastfeeding, inflammatory diseases, perimenopause transition stage;
3. A score of ≥14 on the Beck Depression Inventory II of psychiatric disorders;
4. Neurologic, gastrointestinal and hepatic, cardiovascular, renal, hematologic, respiratory, endocrinological disorders, breast cancer, HIV etc.;
5. Having undergone a PET scanning procedure during the two years prior to the screening visit.

Study design and stimuli

Stimuli consisted of 3 types of film segments with sound designated as "neutral" (N), "low-intensity erotic stimuli" (L) and "high-intensity erotic stimuli" (H). Erotic segments were obtained from 'women-friendly' erotica (Laan et al., 1994). To accommodate power requirements for PET scanning, for each film type four 3-min segments were selected with comparable stimulus content. The neutral film clips were taken from Jewels of the Caribbean Sea, a 1995 National Geographics documentary about marine life in the Caribbean Sea. The low-intensity erotic film clips depicted sexual foreplay, including manual stimulation of the female actor's genitals by the male actor; the high-intensity erotic depicted cunnilingus and intercourse. The sexual film clips were taken from erotic films known to significantly increase vaginal vasocongestion and subjective sexual arousal ("One size fits all" and "The Bridal Shower" by Candida Royalle) with significant differences between the low- and high-intensity segments (Laan et al., 1994). The low-intensity erotic clips have proven to generate significantly less vaginal vasocongestion and subjective sexual arousal than the high-intensity erotic clips (Both et al., 2005).

The visual stimuli were presented to the volunteers using a video screen, which was connected to a computer system. Three stimulus conditions, each consisting of 4 subsequently presented equivalent film clips of the same stimulus type, were created using a Latin Square design, such that a stimulus condition was preceded or succeeded by each of the other stimulus conditions only once. Subjects were randomly assigned to one of these 3 stimulus conditions. The rationale of this design was that it minimized the effects of "subjects" and "order of visual stimuli", which are nuisance variables in the statistical sense.

There were no differences in the light intensity between the low- and high-intensity erotic movies (47 ± 25 Lux and 44 ± 27 Lux respectively), but the neutral movies had a somewhat higher light intensity than the low- and high-intensity erotic movies (95 ± 35 Lux).

Inter-stimulus intervals between film clips were as short as PET scanning allowed, (between 10 and 12 minutes). Immediately after each film clip the volunteers were asked to answer the questions according to the Subjective Experience Questionnaire (SEQ). The SEQ consists of 5 adjectives (anxious, sexually aroused, genitally sexually aroused, sexual desire, and sexual pleasure), preceded by the Dutch translation of the sentence "How did you feel during the film". The items were measured on a 1 (not at all) to 7 (intense) scale. This questionnaire was adapted from existing subjective experience scales, but was rigorously shortened, because administration of lengthy questionnaires was not feasible between PET-scans.

Main Outcome Measures

Data acquisition

A Siemens PET camera (ECAT Exact HR+, Knoxville, TN, USA), in the Nuclear Medicine Department of University Medical Center of Groningen, was used. The PET protocol consisted of 12 separate acquisitions with an interval of 10 to 12 min. Each acquisition scan, with the exception of the first one, consisted of a 30s frame to correct for activity remaining from the previous scan and at T0 a 120s frame started to assess the regional cerebral perfusion. For each scan 500 +/- 50 MBq of [^{15}O]-H_2O was injected intravenously using an automated pump. To correct for attenuation a single transmission scan of 10 min was performed before the actual scanning started. A head shield was used during the whole procedure to minimize the contribution of scattered radiation. After each scan, the position of the head of the subject was checked and restored if necessary.

Each film clip started 1 min before T0 so that steady state was reached when the injected [^{15}O]-H_2O reached the brain. It takes approximately 10s before the activity reaches the brain. Since the correction frame was 30s long, the injection started 20s after the start of the scanner. This delay also allowed for a check on the proper functioning of scanner and activation sequence. The activation sequence was randomized by an established order.

Once individual images were reconstructed and converted into brain volumes, they were further subjected to pre-processing and statistical analysis using Statistical Parametric Mapping (SPM) version 5 software (SPM5) (Wellcome Trust Centre for Neuroimaging, London, United Kingdom). Volumes were motion-corrected so that all PET scans were aligned to a single volume. A mean aligned volume was created at the end of this process, and this volume was used to co-register the anatomical and functional scans. Scans were reconstructed using iterative reconstruction with 4 iterations and 16 subsets, 5 mm Gaussian post-smoothing, brain mode and zoom 2.25 to a matrix of 128*128*63 with all corrections.

Data analysis

First, the PET scans were corrected for remaining activity from the previous scan. Then for each subject between scans head movement was corrected. The mean image was calculated per subject and used for stereotactic normalization to the SPM PET template. The analysis was performed under the assumption that no global changes in blood flow occur. Also, it was assumed that the summed radioactivity as measured with the PET scanner was directly related to the absolute local perfusion so that small changes in activity could be considered to be linear with small changes in absolute perfusion. These two assumptions enabled the global normalization of the

data from activity to an arbitrary mean perfusion value of 50 ml/100 ml tissue/min. After smoothing the images to remove any residual inter-subject anatomical variability the data were subjected to an ANCOVA model which encompasses all relevant exploratory parameters using statistical parametric mapping (SPM) software version from 2005, referred to as SPM5 (Friston KJ et al., 1995a; Friston KJ et al., 1995b).

There were numerous hypotheses for this exploratory study. The key null hypothesis of this study was that there is no difference in the regional cerebral blood flow (rCBF) in the visual cortex in response to high-intensity sexual stimuli compared neutral stimuli ascertained by Positron Emission Tomography (PET) scan. The corresponding alternative hypothesis was that there is a change in regional cerebral blood flow in the visual cortex in response to high-intensity erotic stimuli in comparison to neutral stimuli in the volunteers.

Additional key exploratory hypotheses explored whether there was a difference between stimulus conditions in rCBF with respect to low-intensity erotic vs. neutral stimuli and between low-intensity erotic vs. high-intensity erotic stimuli. All images were realigned with a generic [^{15}O]-H_2O PET image that was stereotaxically registered to the Montreal Neurological Institute (MNI) brain atlas. MNI coordinates were converted into the coordinate system (Lancaster et al., 2000; Talairach J and P, 1988). Anatomical determinations of activations were an automated coordinate-based available in toolboxes of SPM.

Results

Questionnaire results

All subjects were healthy Caucasian Dutch women with a mean age of 30.3 (± 11.5) years and a steady relationship of 7.7 years on average. All of them used oral contraceptives for 6.6 (± 7.4) years. Their average score on the Beck Depression scale was 2.4, the average weight was 69 kg and their average BMI was 22.

After each scan, the volunteers were asked 5 questions regarding the movie they just had watched. Before the subjects were positioned in the scanner, they were informed that these 5 different questions would be asked immediately after each segment. The results show that there was no anxiety effect. Regarding the other 4 questions there were higher scores watching high-intensity erotic than low-intensity erotic movies.

Scanning results

The various comparisons resulted in many activations and de-activations in different parts of the cortex, but in this report we will focus on the visual cortex, i.e. primary, secondary and tertiary visual cortex (BA's 17, 18 and 19).

Activated regions

Contrasts low- and high-intensity erotic versus neutral movies

Both contrasts low- and high-intensity erotic versus neutral movies resulted in relatively minor bilateral activation in the secondary and tertiary visual cortex, involving BA's 18 and 19 but not in the primary visual cortex (BA 17; Figure 1; Table I). The contrast high-intensity erotic versus low-intensity erotic movies did not result in any activation, neither in the primary (BA 17) nor in the secondary and tertiary visual cortices (BA's 18 and 19).

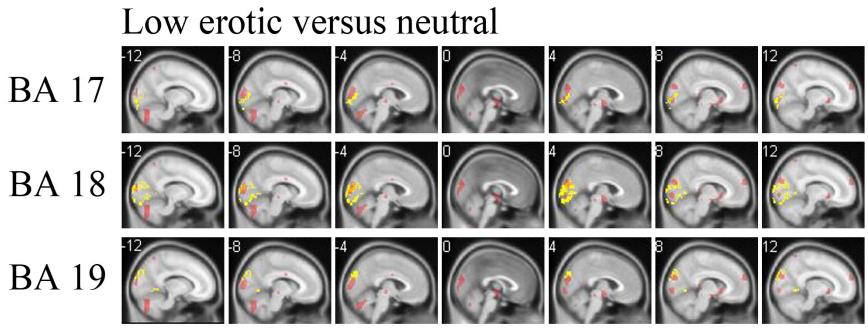

Figure 1. ***Sagittal sections showing the comparison low-intensity erotic versus neutral (p < 0.05 corrected for multiple comparisons) with BA's 17 (top), 18 (middle) and 19 (bottom) indicated in yellow. The activated regions are indicated in red.*** *Note that parts of BA's 18 and 19, but not BA 17 are activated during low-intensity erotic stimuli.*

De-activated regions

Contrast neutral versus low-intensity erotic movies

Although this contrast resulted in large de-activated regions in more frontal parts of the cortex, about which we will report separately, no de-activation was found in the visual cortex (Figure 2).

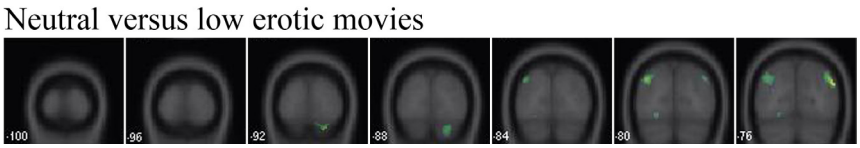

Figure 2. ***Transverse sections, showing the occipital part of cerebral cortex and cerebellum, comparing watching neutral versus low-intensity erotic movies*** *(p < 0.05 corrected for multiple comparisons). Note that de-activated regions do not extend into the visual cortex.*

Brain region	Description	Side	Cluster size	Peak difference			
				Coordinates			Z-score
				x	y	z	
Activation (Low vs High)							
Middle Occipital Gyrus	BA19	L	835	-46	-84	6	6.07
Cuneus	BA18	R	1040	2	-88	20	4.50
Precuneus	*BA19*	*R*		*22*	*-82*	*38*	*4.20*
Cuneus	*BA18*	*L*		*-6*	*-98*	*6*	*4.12*
Activation (High vs Neutral)							
Occipital Lobe	BA19	R	834	10	-92	28	5.32
Deactivation (Neutral vs High)							
Lingual Gyrus	BA18	L	3642	-20	-102	-10	7.97
Cuneus	*BA17*	R		22	-100	-8	7.54
Lingual Gyrus	*BA18*	L		-8	-100	-14	7.03
Deactivation (Low vs High)							
Calcarine	BA17	R	4304	10	-96	-4	7.90
Lingual Gyrus	*BA18*	L		-10	-90	-12	6.26
Middle Occipital Gyrus	*BA18*	R		32	-96	-4	5.92

Table I. ***Activation and de-activation in the visual cortex in different comparisons*** *($p < 0.05$ corrected for multiple comparisons). X, Y, Z coordinates are from the Montreal Neurological Institute (MNI) system. Note that the primary visual cortex showed strong de-activation during high-intensity erotic stimuli compared to neutral as well as low-intensity erotic stimuli.*

Contrast neutral versus high-intensity erotic movies

This contrast, similar to the previous contrast (neutral versus low-intensity erotic movies), also showed strong de-activation in more frontal parts of the cortex, but, different from the previous contrast, a strong bilateral area of de-activation was found in the primary visual cortex (BA 17), extending into the adjoining part of the secondary visual cortex (BA 18), but not in the tertiary visual cortex (BA 19; Figure 3).

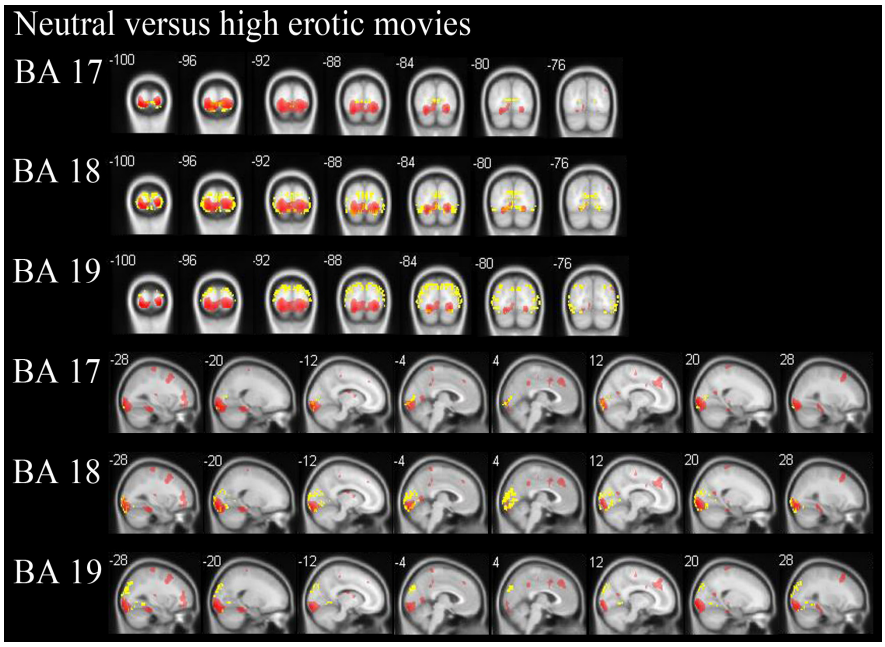

Figure 3. ***Transverse and sagittal sections BA's 17, 18 and 19 are indicated in yellow. The de-activated regions are indicated in red.*** *Note that the primary visual cortex (BA 17) is most strongly de-activated.*

Contrast low-intensity erotic versus high-intensity erotic movies

Comparing watching low-intensity erotic with watching high-intensity erotic movies caused a very strong de-activation of the primary and secondary visual cortex (BA's 17 and 18) bilaterally (Figures 4 and 5). This de-activation is even stronger than in the comparison watching neutral versus high-intensity erotic movies (Table I).

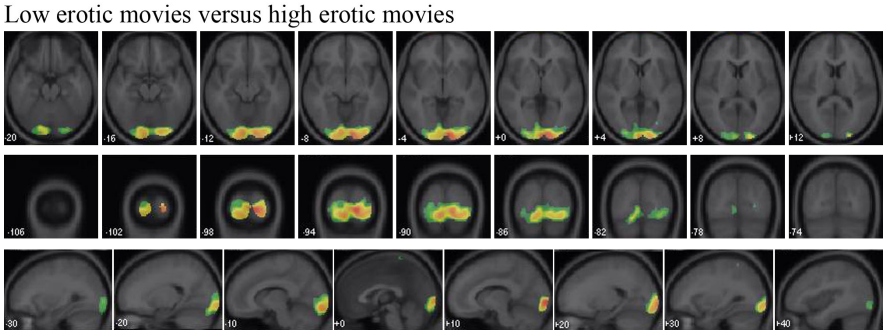

Figure 4. ***Horizontal, transverse, and sagittal sections comparing low-intensity erotic versus high-intensity erotic movies*** *($p < 0.05$ corrected for multiple comparisons). Note that also in this comparison, similar to the comparison neutral versus high-intensity erotic movies, the primary visual cortex (BA 17) is the strongest de-activated region.*

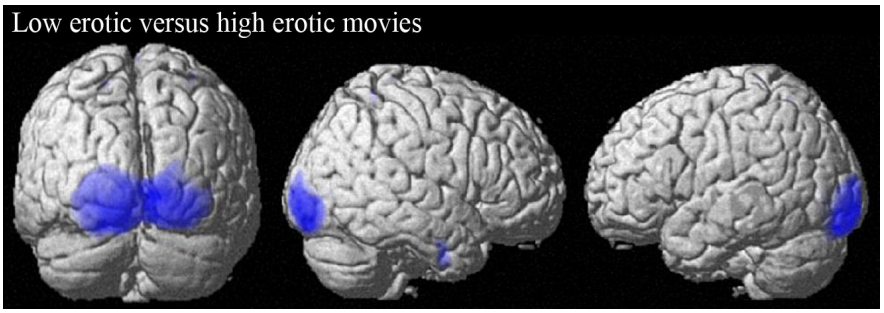

Figure 5. ***De-activation on a volume of rendered brain, comparing watching low-intensity erotic versus high-intensity erotic movies*** *($p < 0.05$ corrected). The primary visual cortex (BA 17) is the most de-activated.*

Discussion

This study shows that high-intensity erotic movies produce an extensive bilateral de-activation of the primary and secondary visual cortex. This is exceptional, because in most neuro-imaging studies in which the volunteers had to watch different non-erotic movies, such de-activation is almost never observed, indicating that the visual cortex was equally active watching these movies.

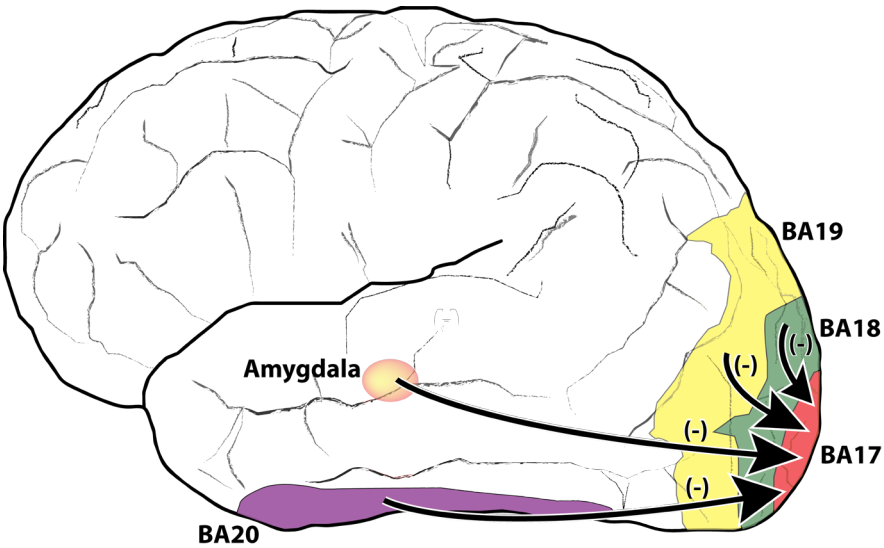

Figure 6. ***Summary diagram of the afferent cortical and amygdalar connections to the primary visual cortex.*** *According to our concept, these regions play a crucial role in causing the de-activation of the primary visual cortex during watching high-intensity erotic movies.*

The fact that we did not find any de-activation of the primary and secondary visual cortex in women watching low intensity erotic movies strongly suggests that the content of the high-intensity erotic movies caused the de-activation. Although such strong de-activation of the visual cortex has never been reported before in women, the Tsujimura group (Miyagawa et al., 2007; Tsujimura et al., 2006), using PET-scanning in men, observed de-activations in the primary visual cortex on the left side, comparing watching mosaic (≈neutral) movies with watching sexually explicit movies. Also Mouras et al. (Mouras et al., 2003), using fMRI scanning in men, observed bilateral de-activation of the primary and secondary visual cortex, watching sexually arousing pictures, but in only 2 of their 8 volunteers.

Not only sexually explicit movies cause de-activation of the primary visual cortex. Azulay et al. (Azulay et al., 2009), who asked the volunteers to perform verbal memory tasks, while watching scrambled visual images of visual objects, also observed robust de-activation in V1. They suggested that this de-activation represents compensation for the increased blood supply necessary in other brain regions in order to perform activities such as verbal memory.

Obviously the female brain considers sexual behavior as a very important task, which deserves high priority, and, similar to verbal memory tasks, the de-activation of V1 might represent compensation for the increased blood supply necessary for other brain regions to perform sexual activity. Another argument might be that during sexual arousal precise verification of the visual field is not necessary.

Which brain regions induce this de-activation?
Considering the outgoing and incoming connections of the primary visual cortex (BA 17), a dorsal and a ventral fiber stream originate in V1. The dorsal stream projects to the parietal lobe and recognizes where objects are in space, the ventral stream projects to the secondary (BA 18) and tertiary visual cortex (BA 19), but also further rostrally to quaternary visual cortex or fusiform gyrus (BA 37) and the inferior temporal cortex (BA 20). These regions identify and recognize the observed objects. Bar et al. (Bar et al., 2006) suggest that there would even exists a direct pathway from the visual to the orbitofrontal cortex, because the projection of visual images of low spatial frequency from the primary and secondary visual cortex reaches the orbitofrontal cortex earlier than it reaches the regions in the temporal lobe.

The other way round, there exist many fiber streams to the primary visual cortex (V1). Best known is the stream from the lateral geniculate thalamic nucleus (Kaas and Huerta, 1988; Kaas et al., 1976), but there are also many fibers coming from the pulvinar thalamic nucleus (Kaas and Huerta, 1988; Ogren and Hendrickson, 1977). From the cortex many fibers termi-

nating in V1 originate in the V2, V3, V4 and V5 visual cortices (Burkhalter and Bernardo, 1989; Cusick and Kaas, 1988; Felleman and Van Essen, 1991; Krubitzer and Kaas, 1990; Krubitzer and Kaas, 1993; Lin et al., 1982; Livingstone and Hubel, 1987; Maunsell and van Essen, 1983; Ungerleider and Desimone, 1986). Although the serotonergic (dorsal raphe nuclei), nor-adrenergic (locus coeruleus) (Koyama et al., 1994) and cholinergic cell groups (basal forebrain) (Herrero et al., 2008) have access to V1, it is unlikely that these projections can produce the de-activation as observed in this study. Perhaps more importantly, also the basal nucleus of the amygdala projects to the primary visual cortex (Freese and Amaral, 2005). It means that large regions of the temporal cortex, including the amygdala, have direct access to the primary visual cortex (Figure 6). Rudrauf and others (Rudrauf et al., 2008) refer to the temporal pole with the amygdala together with the orbitofrontal cortex as the "anterior affective system" (AAS). This AAS is critical for emotion processing, because it not only receives visual afferents, as indicated above, but it also receives visual information via the so-called rapid "alarm system", which involves the optic tract, superior colliculus, pulvinar, amygdala and prefrontal cortex (Liddell et al., 2005). The assessment of the incoming visual information by the AAS not only determines what this visual information represents, but also the eventual impact of this information. Does it contain anything important in the context of the two goals of the brain, survival of the individual and survival of the species? If this is the case, the AAS informs all parts of the brain and brainstem, involved in basic behavior, such as large parts of the prefrontal cortex, cingulate gyrus, anterior temporal lobe, and in the brainstem the periaqueductal gray.

The present results suggest that the content of the visual information, in case of high-intensity erotic movies, causes the AAS to de-activate V1, possibly because these movies do not require precise scanning of the visual field and more blood supply is needed in other parts of the brain.

To conclude, the present study shows that high sexual arousal involves de-activation of primary and secondary visual cortex. In future publications we will present the other areas of the brain that were activated or de-activated with similar sexual stimuli.

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Chapter **4**

Female orgasm but not male ejaculation activates the pituitary. A PET-neuro-imaging study

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Abstract

Introduction. *The pituitary gland plays an important role in basic survival mechanisms by releasing fluctuating amounts of hormones into the bloodstream, depending on the circumstances the individual finds itself. However, despite these changes in pituitary hormonal production, neuroimaging studies have never been able to demonstrate changes in the activation level of the pituitary. The most apparent reason is the much higher blood flow rate in the pituitary than in the brain.*

Aim. *Present PET-scanning study demonstrates for the first time that neuroimaging techniques can identify increased pituitary activity.*

Methods. *Ejaculation in men and orgasm in women was induced by manual stimulation of the penis or clitoris by the participants' partners. Positron emission tomography (PET) with correction for head movements was used to capture the pattern of brain activation at the time of sexual climax.*

Main Outcome Measures*. PET scans showing areas of activation during sexual climax.*

Results. *In a study with 11 healthy women sexual orgasm compared to rest caused an increased blood supply to the pituitary. We assume that this increase signifies elevated pituitary activation in order to produce higher plasma concentrations of oxytocin and prolactin. These hormones induce vaginal and uterus movements, ovulation and enhancement of sperm and egg transport. No increased blood supply was observed comparing clitoral stimulation, orgasm attempt, and faked orgasm with rest.*

Conclusion. *In a study with 11 healthy men comparing ejaculation with rest did not reveal increased pituitary activation, probably because ejaculation causes a much lower increase of oxytocin and prolactin plasma concentration than female orgasm.*

Introduction

In contrast to all other parts of the brain, neuroimaging techniques have never demonstrated any activation or de-activation of the pituitary or hypophysis. The most likely reason is that the pituitary is believed to have the highest blood flow rate of any organ in the body, including the brain. It would explain, assuming that the relative changes in the pituitary are much smaller than in the cerebrum, why changes in the amount of blood passing through the pituitary are too small to be detected by neuroimaging techniques.

The pituitary is an effector organ of the hypothalamus, which plays a crucial role in basic survival mechanisms. The hypothalamic responses on environmental events have a fast and a slow component. For its fast responses the hypothalamus uses its fiber pathways to other parts of the central nervous system such as those to the sympathetic and parasympathetic motoneurons in brainstem and spinal cord (Holstege, 1987). For its slow responses the hypothalamus uses the pituitary. The anterior pituitary or adenohypophysis is non-neural glandular and receives, via the bloodstream entering this part of the pituitary, releasing hormones from various parts of the hypothalamus. Based on these incoming hormones, neurons in the anterior pituitary secrete, among several others, prolactin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the bloodstream. The posterior pituitary (or neurohypophysis) has a more direct connection with the hypothalamus, because it receives fibers from neurons in the paraventricular and supraoptic nuclei of the hypothalamus, which fibers secrete oxytocin and vasopressin into the bloodstream. Although the hypothalamic responses via the pituitary are rather slow, relatively fast events as ejaculation in men, but especially sexual orgasm in women result in fast increases of oxytocin in the peripheral circulation (Blaicher et al., 1999; Carmichael et al., 1987), while vasopressin remains unchanged (Kruger et al., 2003). The plasma concentration of prolactin also increases during sexual arousal and orgasm in men and women (Exton et al., 1999; Kruger et al., 2003), while LH increases to a limited extent and FSH remains the same (Exton et al., 1999). These relatively fast changes in hormonal plasma concentrations elicited by female orgasm can only be caused by fast changes in activation of the pituitary. Although one might expect to detect such changes in pituitary activation using neuroimaging, in two previous PET-scanning studies on male ejaculation and female orgasm (Georgiadis et al., 2006; Holstege et al., 2003), no changes in pituitary function were observed. A method for correcting head movements allowed us to more precisely identify activations and de-activations in the various brain regions including the pituitary.

Materials & Methods

Participants

Eleven healthy right-handed heterosexual female participants (between 21 and 47 years old, mean age 33) with their male partners and eleven healthy right-handed heterosexual males (between 19 and 45 years old, mean age 34) with their female partners were selected. All participants submitted written informed consent according to the Declaration of Helsinki. The Medical Research Ethics Committee of the University Medical Center and University of Groningen approved the study. None of the participants had any history of physical, psychiatric, or sexual disorders. All participants, regardless of their performance, received a modest reimbursement of travel expenses.

Study design

Eleven women were asked to perform the following tasks (Figure 1 top):
1.Rest (passive non-sexual resting state) once;
2.Faking or imitating orgasm (voluntary repetitive contractions of coxeal, gluteal, abdominal and pelvic floor muscles in a rhythmic 'orgasm-like' fashion, while receiving stimulation of the clitoris) twice;
3.Clitoral stimulation (receiving clitoral stimulation without executing bodily movements) twice;
4.Sexual orgasm, once, twice or three times with rectal pressure recorded in order to ascertain the orgasms were real.

Reported orgasms were included if they met the following criteria:
a.According to the participant, orgasm was definite and occurred in the first minute of the scan;
b.The orgasm report was supported by the rectal pressure pattern of the same scan;
c.The rectal pressure pattern of a reported orgasm and that of an imitation of orgasm (task 2) were clearly distinct, because both involve contraction of the same muscles, but with different frequency characteristics (Bohlen et al., 1982).

The male participants were asked to perform the following tasks twice (Figure 1 bottom):
1.Rest (passive nonsexual resting state);
2.Erection (after receiving penile stimulation without executing bodily movements);
3.Sexual stimulation (after receiving penile stimulation without executing bodily movements);
4.Ejaculation induced by sexual stimulation.

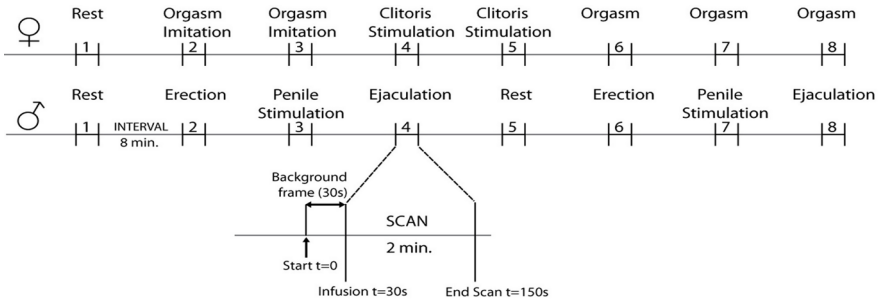

Figure 1. ***The tasks of the female (top) and the male (bottom) volunteers.*** *Although orgasm and ejaculation tasks were possible more than once, in most successful cases it occurred only once.*

To minimize motor activity by the participant during the scan, her/his male/female partner provided the sexual stimulation by means of manual clitoris/penile stimulation during the tasks stimulation and orgasm/ejaculation. Manual stimulation was continued throughout orgasm/ejaculation. To minimize head motion a head-restraining adhesive band was used, and, in order to minimize visual input, participants were asked to keep their eyes closed.

In the week before the experiments, the participants and their male/female partners were informed about how the experiments would be conducted, and were asked to practice at home, especially regarding minimizing head and limb movements. Before the experiment, the precise procedure was again extensively discussed with the participants and their partners. Great effort was made to let the participants feel relaxed during the experiments. When asked for their emotional experiences during the tasks, the participants did not report important differences between their sexual experiences under normal circumstances at home and in the scanner. All male participants reported to have used visual imagery to better perform the tasks, and that stimulation, ejaculation, and real female orgasm were accompanied by pleasurable sensations.

PET protocol

Measurements were made with a CTI/Siemens Ecat Exact HR+ scanner (CTI/Siemens, Knoxville TN, USA). This 32 ring PET scanner with an axial field of view of 15.5 cm, operated in 3D-mode to have maximum sensitivity, simultaneously images a total of 63 planes with a spatial resolution of 4–5 mm full width at half maximum (FWHM) in all three directions. The tracer [^{15}O]-H_2O was used to measure regional cerebral blood flow (rCBF). To allow for the decay of the [^{15}O]-H_2O (half-life 122 seconds), successive scans were made with an interval of 8 minutes. For each scan 500 MBq of [^{15}O]-H_2O was injected into the right median antebrachial vein and flushed

with saline with a total volume of 32 ml at a speed of 8 ml/s. Except for the first scan, PET-scanning began 30 seconds prior to the injection in order to acquire background correction information and was continued for an additional two minutes to measure brain uptake. The injection of the radioactive bolus was timed such that the activity entered the brain in the first few seconds of the two minutes period. Because [^{15}O]-H_2O has an extraction fraction of 100%, the brain uptake is mainly determined by the period in which the plasma activity concentration is high i.e. in the first minute after it initially entered the brain. Consequently, the participants aimed to ejaculate or have an orgasm within this first minute.

Data processing and statistical analysis

As could be expected, the participants made more head movements during the ejaculation/orgasm task than usually during PET-scan studies. For this reason, unlike the previous studies (Georgiadis et al., 2006; Holstege et al., 2003), all individual frames of the 120s-images of male and female stimulation, male ejaculation and female orgasm were corrected for motion during the scan before the standard data processing. This was performed in SPM8 by a rigid-body realignment of the individual frames to the last frame of the series. Occasionally, the first very short frames did not contain enough counts for a reliable realignment. In this case realignment parameters were obtained by extrapolation. The motion corrected frames were then summed for subsequent standard processing in SPM8 (Figure 2). Note that (head) motion during the PET scans introduces a mismatch between the emission data (the activity in the brain) and the transmission scans (used to correct for photon attenuation in the brain) which is not compensated for in this study.

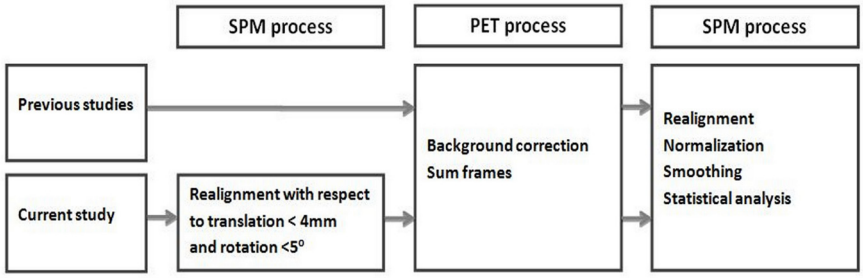

Figure 2. ***The difference in the data processing and statistical analysis in the present study compared to the two previous studies*** *(Holstege et al. 2003; Georgiadis et al. 2006).*

Once individual images were reconstructed and converted into brain volumes, they were further subjected to pre-processing and statistical analysis using SPM8 (Friston KJ et al., 1995a; Friston KJ et al., 1995b; Talairach J and P,

1988). The data were realigned, stereotactically normalized into Montreal Neurological Institute (MNI) space, and, to increase the signal-to-noise ratio and to minimize the effect of residual errors in stereotactic normalization, the data were smoothed using an isotropic Gaussian kernel of 10 mm FWHM. An analysis of variance (ANOVA) with participant and experimental condition as factors, leaving 52 degrees of freedom, was performed on the data to estimate the parameters. The data were normalized for global effects by means of proportional scaling.

Differences in regional cerebral activity due to sexual stimulation of the clitoris/penis were tested by performing a Student's t-test on each voxel (2x2x 2 mm) of the brain, testing against the null hypothesis of no difference. We investigated rCBF increases (Activations: stimulation scans minus rest scans) testing the parameter contrast at $p<0.001$.

Clusters of at least 5 voxels that were significantly activated ($p<0.001$, uncorrected) are reported. MNI coordinates were converted into the coordinate system of the Talairach and Tournoux stereotaxic atlas (Chau and McIntosh, 2005; Talairach J and P, 1988). Anatomical determinations of activations were made by xjView, an automated coordinate-based Talairach and MNI labeling system and by a viewing program for SPM. We used the region of interest analysis MarsBars toolbox for SPM (http://marsbar.sourceforge.net) to calculate the contrast of rCBF in pituitary in different conditions comparing to Rest conditions.

Results

The present results differ from the two previous studies on men ejaculation and women's orgasm (Georgiadis et al., 2006; Holstege et al., 2003), because they have been corrected for head movements as indicated above (Figure 2). To remove this source of artifact, all individual frames of the 120s-images captured during male and female stimulation, male ejaculation and female orgasm were corrected for motion during the scan. Basically, the results did not contradict the results of the two previous studies, in the sense that activations were observed in basically the same brain regions. However, in this study the activated and de-activated regions were much more precisely delineated, and activations were also observed in the pituitary. In this manuscript we will only report and discuss the results for the pituitary and hypothalamus.
In men comparing ejaculation with rest or penile stimulation did not reveal any significant increased activation in either the pituitary (Figure 3A) or hypothalamus. On the other hand, in women, comparing real orgasm with rest ($p<0.001$), a clear significant increased rCBF was observed in

the pituitary (Figures 3B, 4 and 5). The comparison orgasm with clitoral stimulation ($p<0.001$) revealed an even stronger increased pituitary activation than the comparison orgasm with rest (Figure 3C), albeit that this difference was not statistically significant. The reason is that clitoral stimulation, compared with rest, resulted in a slight non-significant decrease of rCBF in the pituitary (Figure 4). Neither in men nor in women any significant activation or de-activation was found in the hypothalamus. In that respect possible activation of the paraventricular and pre-optic nuclei, the two nuclei that send fibers to the posterior pituitary, represent only a small portion of the total hypothalamus, which might be the reason that eventual increased rCBF in these nuclei is too small to be detected by PET-scan techniques. On the other hand, Komisaruk and others in an fMRI-study showed activation of the region of the paraventricular nucleus during orgasm in women, but not in the pituitary (Komisaruk et al., 2004). Comparing failed orgasm and faking orgasm with rest ($p<0.001$) did not result in a significant rCBF increase in the pituitary (Figure 3E, F).

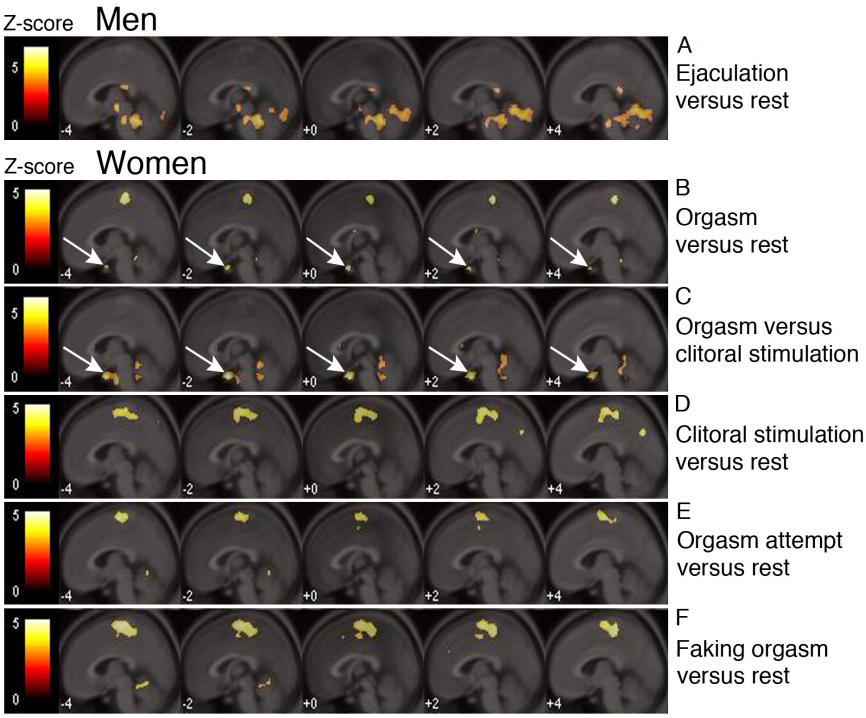

Figure 3. *Sagittal sections showing in A that in men the comparison ejaculation versus rest resulted in activation in several brain regions, but not in the pituitary. In women the comparisons orgasm versus rest (B) and orgasm versus clitoral stimulation (C) show clear activation in the pituitary (see arrows). In the other comparisons (D, E and F) no significantly increased rCBF could be observed in the pituitary.*

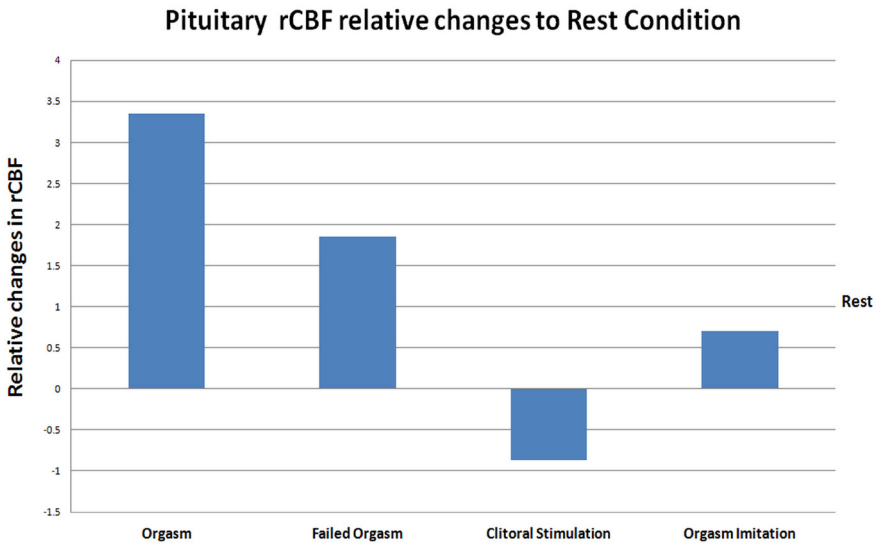

Figure 4. ***Regioanal Cerebral Blood Flow (rCBF) relative changes to rest in the pituitary*** *using the MarsBaR region of interest toolbox for SPM.*

Pituitary activation (p<0.001)

Contrast	Cluster size	Peak difference Coordinates			Z-score
		x	y	z	
Orgasm - Rest	42	2	6	-30	4,28
Orgasm - Clitoris stimulation	131	-2	4	-26	6,3

Figure 5. ***Cluster size, coordinates and Z-scores of pituitary activation.***

Discussion

This is the first neuroimaging study that shows pituitary activation. The reason that such activation was not found in other studies might be that the pituitary blood flow is much higher than in the brain. In sheep, for example, is the pituitary blood flow eight times higher than in the cerebral cortex (Page et al., 1981). It would mean that the same change in blood supply, that can be identified in the cerebral cortex using fMRI of PET-scanning, cannot be detected in the pituitary, because percentagewise this change is much smaller. In that case only relatively large changes in the pituitary blood supply can be detected by neuro-imaging techniques. Such large changes do not take place during the tasks performed by the volunteers in most neuroimaging studies. However, during female sexual orgasm or male ejaculation larger changes in rCBF occur. In this study, significant

rCBF increase was observed in women, but not in men. This finding corresponds with the fact that the increase of the release of oxytocin into the bloodstream after orgasm or ejaculation is much higher in women than in men (Exton et al., 1999; Kruger et al., 2003). According to Carmichael and others, oxytocin plays an important role in sexual function (Carmichael et al., 1987). Oxytocin plasma levels correspond with the lordosis response in rats as well as with the intensity of muscular contractions during orgasm in men and women (Pedersen and Boccia, 2002, 2006; Sansone and Komisaruk, 2001). Intranasal administration of synthetic oxytocin is used to help breastfeeding, vaginal lubrication and vaginal contraction to improve sexual pleasure in women (Anderson-Hunt and Dennerstein, 1994, 1995).
The anterior pituitary gland releases prolactin, a pleiotropic neuroendocrine hormone involved in many biological functions including sexual behavior (Freeman et al., 2000; Garzia et al., 2004; Grattan and Kokay, 2008; Jabbour and Critchley, 2001). Also prolactin plasma levels have been shown to have increased significantly after orgasm in women and ejaculation in men, albeit to a much lesser extent in men (Brody and Kruger, 2006; Exton et al., 1999; Exton et al., 2001; Kruger et al., 2003; Kruger et al., 2012). It corresponds with our finding that a significant increase in rCBF could not be demonstrated in the pituitary during male ejaculation. Egli and others suggested that prolactin plays an important role in the female orgasm induced neuroendocrine reflex, optimizing fertility and conception (Egli et al., 2010).

PET brain activation studies using rCBF measurements are based on the premise that changes in regional blood flow are correlated with changes in neuronal firing. This is corroborated by the fact that cerebral blood flow is tightly controlled via an autoregulatory system, irrespective of the systemic pressure (Paulson et al., 1990). In the rat autoregulation in the adenohypophysis is not as tightly controlled as in the brain (Kemeny et al., 1985). If so one might argue that an increase in pituitary blood flow might be caused by an increase in overall increase in blood flow during orgasm rather than an increased neuronal activity. However, although the cardiac output of the subjects during the acquisition of the PET scan, was not measured, it is well known that blood pressure and heart rate during orgasm are well within the range of the daily-life workload and that the metabolic equivalent of energy expenditure during orgasm is relatively modest (Drory et al., 1996; Palmeri et al., 2007; Xue-Rui et al., 2008).
Also age, sex and diurnal and ovulatory cycle may affect hormonal release by the pituitary, while pituitary size and function may also fluctuate considerably. Yet, it is unlikely that inclusion of additional confounding parameters would have a large effect on our results, because this group study is based on within subject contrasts i.e. each subject is compared to itself and only common effects are retained.
In conclusion, despite the limitations of this study, the pituitary activation

found is indeed linked to an increase in pituitary function. This supports the link between the release of prolactin and oxytocin and sexual behavior (Anderson-Hunt and Dennerstein, 1994, 1995; Donner and Neumann, 2009; Freeman et al., 2000; Garzia et al., 2004; Grattan and Kokay, 2008; Jabbour and Critchley, 2001; Murphy et al., 1987). This role is further supported by our finding that failed orgasm (orgasm attempt) or faking (imitating) orgasm did not produce a significant rCBF increase in the pituitary.

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Chapter 5

Pontine control of ejaculation and female orgasm

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Abstract

Introduction. *The physiological component of ejaculation shows parallels with micturition since both are essentially voiding activities. Both depend on supraspinal influences to orchestrate the characteristic pattern of activity in the pelvic organs. Unlike micturition, little is known about the supraspinal pathways involved in ejaculation and female orgasm.*
Aim. *To identify brainstem regions activated during ejaculation and female orgasm and to compare them with micturition.*
Methods*. Ejaculation in men and orgasm in women was induced by manual stimulation of the penis or clitoris by the participants' partners. Positron emission tomography (PET) with correction for head movements was used to capture the pattern of brain activation at the time of sexual climax.*
Main Outcome Measures. *PET scans showing areas of activation during sexual climax.*
Results*. Ejaculation in men and orgasm in women resulted in activation in a localized region within the dorsolateral pontine tegmentum on the left side and in another region in the ventrolateral pontine tegmentum on the right side. The dorsolateral pontine area was also active in women who attempted but failed to have an orgasm and in women who faked orgasm. The ventrolateral pontine area was only activated during ejaculation and physical orgasm in women.*
Conclusion. *Activation of a localized region on the left side in the dorsolateral pontine tegmentum, which we termed the pelvic organ stimulating center (POSC) occurs during ejaculation and physical orgasm in women. This same region, but on the right side, has previously been shown to be activated during micturition. The POSC, via projections to the sacral parasympathetic motoneurons, controls pelvic organs involved in voiding functions. In contrast, the ventrolateral pontine area, which we term pelvic floor stimulating center (PFSC), produces the pelvic floor contractions during ejaculation and physical orgasm in women via direct projections to pelvic floor motoneurons.*

Introduction

Ejaculation is a key event and end point in male sexual activity. At the climax of coitus ejaculation propels seminal fluid containing sperm through the urethra and into the female vagina, the biological objective being to fertilize a female ovum. This event is effected by a highly synchronized pattern of rhythmic contractions of smooth and striated muscles within the pelvic region.

Ejaculation consists of two phases: emission and expulsion. Spermatozoa are made in the testes and are stored in immature form in the epididymis, which lies on the posterior surface of the testicles. During the emission phase, which accompanies arousal and penile erection, both sympathetic and parasympathetic tones act in a synergistic fashion to initiate seminal emission by activating respectively smooth muscle contraction and epithelial secretion throughout the seminal tract (Giuliano and Clement, 2005). The seminal vesicles, prostate and vas deferens facilitate transfer of their respective contents into the prostatic urethra to mix with sperm to form the seminal fluid (Giuliano and Clement, 2005). At the same time the bladder neck contracts to prevent the backflow of sperm into the bladder (Giuliano, 2011; Peeters and Giuliano, 2008). During the expulsion phase, powerful rhythmic contractions of the bulbospongiosus muscle, together with synchronized contraction of the ischiocavernosus and levator ani muscles, propel the semen through the urethra to exit the body via the urethral meatus (Carro-Juarez and Rodriguez-Manzo, 2008; Coolen et al., 2004; McKenna et al., 1991). The process is mediated via the synchronized activity of the sympathetic, parasympathetic and somatic nerves (Courtois et al., 2013; Giuliano, 2011; Johnson, 2006).

Although ejaculation is considered primarily a male event, a homologue exists in females. During orgasm, the vaginal smooth muscle and the striated bulbospongiosus muscle produce rhythmic contractions in the distal part of the vagina to draw semen into the vagina, making it easier for sperm to approach and fertilize the egg (Bohlen et al., 1980; Bohlen et al., 1982; Carmichael et al., 1987; Carmichael et al., 1994; Kratochvil, 1994; Masters and Johnson, 1966). Some women also experience expulsion of various quantities of fluids that originate from the female prostate (Skene's glands), the urinary bladder or a combination of both (Pastor, 2013). Expulsion of prostatic secretions is considered to represent true female ejaculation whilst urine-containing fluid ejected during "squirting" is a form of coital urinary stress-incontinence, i.e. a pathophysiological event (Pastor, 2013).

In conscious humans the events described above in males and females, are accompanied by intensely pleasurable sensations known as orgasm.

In male animals at least, ejaculation is a positively reinforcing experience, which implies that it is also associated with pleasurable or rewarding sensations (Pfaus et al., 2001; Pfaus et al., 2012). Ejaculation can therefore be considered as a physiological event, which is accompanied by a positively rewarding emotional experience. Separate terms have not been coined for these two events in women, but we will hereafter refer to them as physical and emotional orgasm, of which the former shows some parallels with ejaculation.

In spinal cord-injured humans and animals, portions of these sexual responses are lost when the lesion severs ascending pathways to the brainstem and higher centers, and descending pathways from the brainstem and higher centers to the spinal cord. However, even though normal ejaculation is severely impaired or absent in men after spinal transection, it still can be triggered by extremely intense supraphysiological levels of stimulation (Brackett et al., 1997; Sonksen et al., 1994; Sonksen and Ohl, 2002). This finding suggests that ejaculation may be primarily a spinal reflex response, albeit one that under normal conditions is dependent on modulating or permissive influences from the brain. Thus the segmental circuits require a long loop connection to maintain their function.

Our current understanding of the spinal ejaculation circuitry is derived primarily from functional studies on rats. Within the L3-L5 spinal segments a group of neurons in Rexed's laminae VII and X have been identified as a spinal generator for ejaculation. It has been suggested that these cells co-ordinate the various aspects of ejaculation described above (Xu et al., 2006). In addition they transmit sensory information specifically linked to ejaculation (rather than other aspects of sexual activity) to thalamic sites and integrate information descending from higher centers (Borgdorff et al., 2008; Truitt et al., 2003). After spinal transection the functional integrity of these cells is essential for ejaculation to take place (Staudt et al., 2012).

Although it is clear that ejaculation is normally dependent on activation of a supraspinal loop, relatively little is known about the brain areas that control ejaculation. Several regions have been shown to exert facilitatory or inhibitory controls on the spinal centers for ejaculation (Coolen et al., 2004). The ventromedial medulla exerts an inhibitory influence on ejaculation (Marson and McKenna, 1992). The cells in this region are activated by afferent input from the penis but only after repetitive penile stimulation as occurs during intromission (Hubscher and Johnson, 1996). Johnson suggested that activation of this pathway ensures the periodic presynaptic inhibition of excitatory penile afferent input, in order to maintain the proper sequence of propulsive contraction bursts of m.bulbospongiosus interfaced with closure of the bladder neck and emission of semen (Johnson, 2006). However, it is also well established that the ventromedial medulla projects

non-specifically to all motor areas of the spinal cord (Holstege, 1991). These cells are thought to set the level of excitability of spinal motor functions in general, including those of the pelvic floor that are engaged during ejaculation.

In addition excitatory influences arise further rostrally, from several regions of the hypothalamus, the medial preoptic area (Markowski et al., 1994; Pehek et al., 1989; Robinson and Mishkin, 1966), the paraventricular nucleus (Marson and McKenna, 1994), and the lateral hypothalamus (Kippin et al., 2004). Of these, only the PVN projects to the spinal cord directly. The other regions must therefore access the spinal circuitry via an indirect route (Marson and Foley, 2004).

The physiological component of ejaculation shows parallels with micturition since both are essentially voiding activities. Indeed both the bladder and epididymis utilize the urethra as the final conduit for ejection of fluids (urine and semen respectively). Studies in animals have shown that micturition is dependent on the integrity of a spino-brainstem-spinal loop, which has relays in the midbrain periaqueductal gray and thereafter to a region in the dorsolateral pontine tegmentum known as the pontine micturition centre (PMC) (de Groat, 2006; Drake et al., 2010; Holstege, 2005b, 2010; Holstege et al., 1986). In humans too (men and women) neuroimaging studies have demonstrated that during micturition a region in the pons, corresponding to the PMC, is activated (Blok et al., 1997a, 1998; Blok et al., 1997b). Animal studies have shown that the PMC not only projects to the parasympathetic motoneurons innervating the bladder, but also to the parasympathetic motoneurons innervating the other pelvic organs (Blok and Holstege, 1997; Holstege et al., 1986; Holstege and Kuypers, 1982; Holstege et al., 1979; Nuding and Nadelhaft, 1998). It seems plausible, given the parallels between micturition and ejaculation in terms of voiding activities, to speculate that the PMC region may play a role in controlling ejaculation too.

In a previous study using positron emission tomography in humans we showed that ejaculation was accompanied by widespread activation and de-activation of forebrain structures. In addition, there was intense activation in the rostral mesencephalon (Holstege et al., 2003), which may represent the conduit via which forebrain structures access the cord. The resolution of the images captured in our early study was limited due to the involuntary head movements made by the participants during ejaculation. We have now re-analyzed these data on a frame-by-frame basis to correct for head movements. This has improved significantly the spatial resolution of the data and enabled us to localize more precisely the anatomical substrate for the pontine involvement in ejaculation. The results suggest that a region in the dorsolateral pontine tegmentum equivalent to the PMC, is an integral

part of the ejaculation control circuitry. In view of the activation of this region during micturition we propose that the PMC should be re-named as the pelvic organ stimulating centre (POSC).

Methods

Participants

Eleven healthy right-handed heterosexual female participants (between 21 and 47 years old, mean age 33) with their male partners and eleven healthy right-handed heterosexual males (between 19 and 45 years old, mean age 34) with their female partners were selected. All participants submitted written informed consent according to the Declaration of Helsinki. The Medical Research Ethics Committee of the University Medical Center and University of Groningen approved the study. None of the participants had any history of physical, psychiatric, or sexual disorders. All participants, regardless of their performance, received a modest reimbursement of travel expenses.

Study design

Eleven women were asked to perform the following tasks (Figure 1 top):
1.Rest (passive non-sexual resting state) once;
2.Faking or imitating orgasm (voluntary repetitive contractions of coccygeal, gluteal, abdominal and pelvic floor muscles in a rhythmic 'orgasm-like' fashion, while receiving stimulation of the clitoris) twice;
3.Clitoral stimulation (receiving clitoral stimulation without executing bodily movements) twice;
4.Sexual orgasm, once, twice or three times with rectal pressure recorded in order to ascertain the orgasms were real.

Reported orgasms were included if they met the following criteria:
a.According to the participant, orgasm was definite and occurred in the first minute of the scan;
b.The orgasm report was supported by the rectal pressure pattern of the same scan;
c.The rectal pressure pattern of a reported orgasm and that of an imitation of orgasm (task 2) were clearly distinct, because both involve contraction of the same muscles, but with different frequency characteristics (Bohlen et al., 1982).

The male participants were asked to perform the following tasks twice (Figure 1 bottom):

1.Rest (passive nonsexual resting state);
2.Erection (after receiving penile stimulation without executing bodily movements);
3.Sexual stimulation (after receiving penile stimulation without executing bodily movements);
4.Ejaculation induced by sexual stimulation.

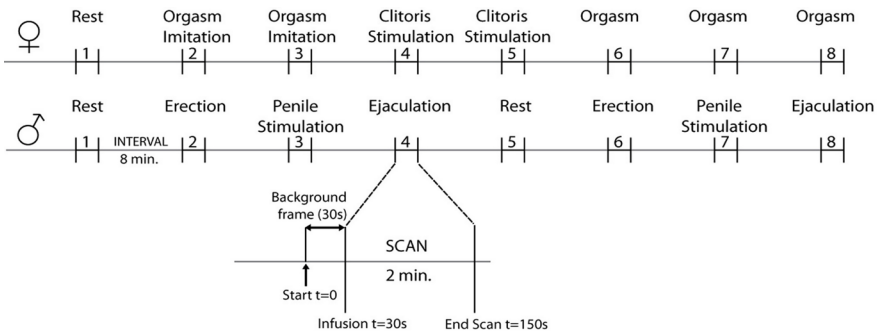

Figure 1. ***Framework of experiments of eleven female (above) and eleven male (bottom) volunteers.*** *Although some individuals were able to perform orgasm and ejaculation tasks more than once, in most successful cases it occurred only once. Note the first scan does not have a background frame.*

To minimize motor activity by the participant during the scan, her/his male/female partner provided the sexual stimulation by means of manual clitoris/penile stimulation during the tasks stimulation and orgasm/ejaculation. Manual stimulation was continued throughout orgasm/ejaculation. To minimize head motion a head-restraining adhesive band was used, and, in order to minimize visual input, participants were asked to keep their eyes closed.

In the week before the experiments, the participants and their male/female partners were informed about how the experiments would be conducted, and were asked to practice at home, especially regarding minimizing head and limb movements. Before the experiment, the precise procedure was again extensively discussed with the participants and their partners. Great effort was made to let the participants feel relaxed during the experiments. When asked for their emotional experiences during the tasks, the participants did not report important differences between their sexual experiences under normal circumstances at home and in the scanner. All male participants reported to have used visual imagery to better perform the tasks, and that stimulation, ejaculation, and real female orgasm were accompanied by pleasurable sensations.

Main Outcome Measures

PET protocol

Measurements were made with a CTI/Siemens Ecat Exact HR+ scanner (CTI/Siemens, Knoxville TN, USA). This 32 ring PET scanner with an axial field of view of 15.5 cm, operated in 3D-mode to have maximum sensitivity, simultaneously images a total of 63 planes with a spatial resolution of 4–5 mm full width at half maximum (FWHM) in all three directions. The tracer [^{15}O]-H_2O was used to measure regional cerebral blood flow (rCBF). The [^{15}O]-H_2O (oxygen-15 labelled water) was created in target. After filtration the labeled water was available for injection. Typical times between preparation and injection were 2 to 4 min.

To allow for the decay of the [^{15}O]-H_2O (half-life 122 seconds), successive scans were made with an interval of 8 minutes. For each scan 500 MBq of [^{15}O]-H_2O was injected into the right median antebrachial vein and flushed with saline with a total volume of 32 ml at a speed of 8 ml/s. Except for the first scan, PET-scanning began 30 seconds prior to the injection in order to acquire background correction information and was continued for an additional two minutes to measure brain uptake. The injection of the radioactive bolus was timed such that the activity entered the brain in the first few seconds of the two minutes period. Because [^{15}O]-H_2O has an extraction fraction of 100%, the brain uptake is mainly determined by the period in which the plasma activity concentration is high i.e. in the first minute after it initially entered the brain. Consequently, the participants aimed to ejaculate or have an orgasm within this first minute.

Data processing and statistical analysis

As could be expected, the participants made more head movements during the ejaculation/orgasm task than usually during PET-scan studies. For this reason, unlike the previous studies (Georgiadis et al., 2006; Holstege et al., 2003), all individual frames of the 120s-images of male and female stimulation, male ejaculation and female orgasm were corrected for motion during the scan before the standard data processing. This was performed in SPM8 by a rigid-body realignment of the individual frames to the last frame of the series. Occasionally, the first very short frames did not contain enough counts for a reliable realignment. In this case realignment parameters were obtained by extrapolation. The motion corrected frames were then summed for subsequent standard processing in SPM8 (Figure 2). Note that (head) motion during the PET scans introduces a mismatch between the emission data (the activity in the brain) and the transmission scans (used to correct for photon attenuation in the brain) which is not compensated for in this study.

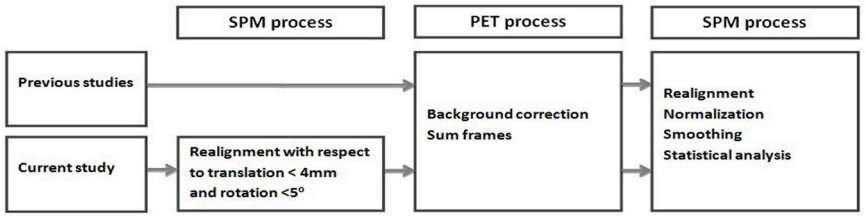

Figure 2. ***Protocol for data processing and statistical analysis with correction for head movements used in the present study in comparison to previous studies*** *(Holstege et al. 2003; Georgiadis et al. 2006).*

Once individual images were reconstructed and converted into brain volumes, they were further subjected to pre-processing and statistical analysis using SPM8 (Friston KJ et al., 1995a; Friston KJ et al., 1995b; Talairach J and P, 1988). The data were realigned, stereotactically normalized into Montreal Neurological Institute (MNI) space, and, to increase the signal-to-noise ratio and to minimize the effect of residual errors in stereotactic normalization, the data were smoothed using an isotropic Gaussian kernel of 10 mm FWHM. An analysis of variance (ANOVA) with participant and experimental condition as factors, leaving 52 degrees of freedom, was performed on the data to estimate the parameters. The data were normalized for global effects by means of proportional scaling.

In this study differences in regional cerebral activity in the entire pons due to sexual stimulation of the clitoris/penis were tested by performing a Student's t-test on each voxel (2x2x2 mm) of the brain, testing against the null hypothesis of no difference. We investigated rCBF increases (activations: stimulation scans minus rest scans). The images shown in the manuscript are at p<0.001, uncorrected for multiple

comparisons. After correction for multiple comparisons (P<0.05), the men results were also significant, but in women, as noticeable in the figures, the activation, although in the same regions, is less strong. The activation in the POSC in women almost reached significance (p<0.10), whereas for the activation in the PFSC a trend towards significance was observed (p<0.25). Another reason for the lower significance in women is that neither in men nor in women both areas were not defined a-priori, so that the correction for multiple comparisons needed to be performed for the whole brain rather than for the pons only, resulting in a lower level of significance.

Clusters of at least 5 voxels that were significantly activated (p<0.001, uncorrected) are reported. MNI coordinates were converted into the coordinate system of the Talairach and Tournoux stereotaxic atlas (Chau and McIntosh, 2005; Talairach J and P, 1988). Anatomical determinations of activations were made by xjView, an automated coordinate-based Talairach

and MNI labeling system and by a viewing program for SPM. We used the region of interest analysis MarsBars toolbox for SPM (http://marsbar.sourceforge.net) to calculate the contrast of rCBF in pituitary in different conditions comparing to Rest conditions.

Results

Of the 20 ejaculation attempts in the male volunteers 13 were successful. Five men could achieve ejaculation twice, three men achieved one ejaculation, and three men could not achieve ejaculation. Of the 31 orgasm attempts in the female volunteers 18 were successful. Six women reached one orgasm, three women reached two orgasms and two women reached three orgasms.

In men as well as in women the comparison ejaculation versus rest revealed many activated and de-activated regions in the cerebral cortex as well as in di-encephalic regions and upper part of the midbrain (Holstege et al., 2003). However, in this paper we will describe only our findings in the lower brainstem, and in particular in the pontine tegmental field. Comparing ejaculation with rest in men and orgasm with rest in women revealed two regions of increased rCBF, one in the dorsolateral pontine tegmentum on the left side and one in the ventrolateral pontine tegmentum on the right side. These activated regions were larger in men than in women (Figure 3; Figure 4 top; Figure 5 top; Figure 6), but the same pattern of activation was observed in all subjects. Data from all same sex subjects was therefore grouped for analysis. In men the activated region in the left dorsolateral pontine tegmentum extended into the cerebellum, which is also strongly activated during ejaculation, mainly on the left side (Holstege et al., 2003). Importantly, no activation in the dorsolateral pontine tegmentum was found when comparing penile stimulation with rest (Figure 4 middle), indicating that the activation seen in the pons is ejaculation-specific.

Contrast	Brain region	Description	Side	Cluster size	Peak difference			
					Coordinates			Z-score
					x	y	z	
Ejaculation-Rest	Pons	PFSC	R	95	6	-20	-30	4.88
Ejaculation-Rest	Pons	POSC	L	2324	-12	-35	-30	5.09
Orgasm-Rest	Pons	PFSC	R	15	12	-20	-30	3.79
Orgasm-Rest	Pons	POSC	L	145	-10	-38	-30	3.94

Figure 3. ***The coordinates and Z-scores of the activation of the pelvic organ stimulation center (POSC) and the pontine pelvic floor stimulation center (PFSC).***

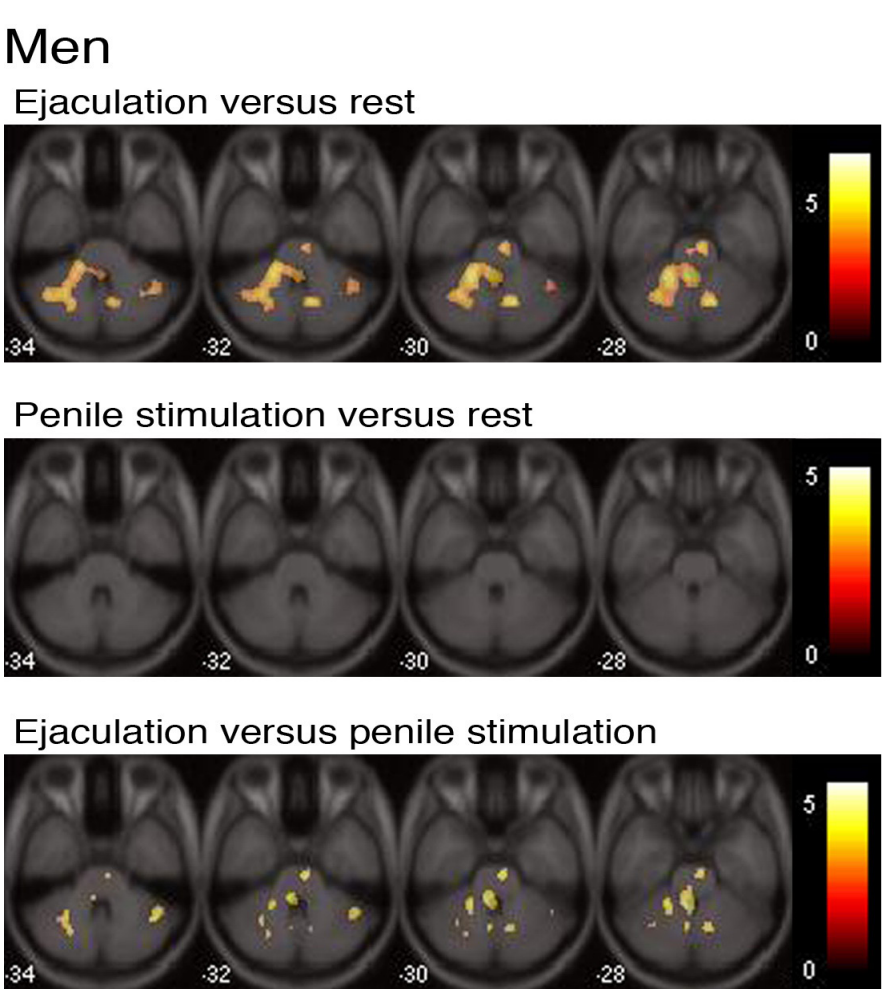

Figure 4. ***Axial plane sections (z=-34 to z=-28) of the brain in men showing the activated regions.*** *Top: during ejaculation compared to rest. Middle: penile stimulation versus rest. Bottom: Ejaculation versus penile stimulation. During ejaculation there was strong activation of the area of the POSC and adjoining parts of the cerebellum on the left and the activated region in the ventrolateral pontine tegmentum on the right. The weaker signal after subtracting the signal evoked during penile stimulation (bottom row of images) indicates that penile stimulation evoked a low level of activation, which did not result in significant activation using our criteria.*

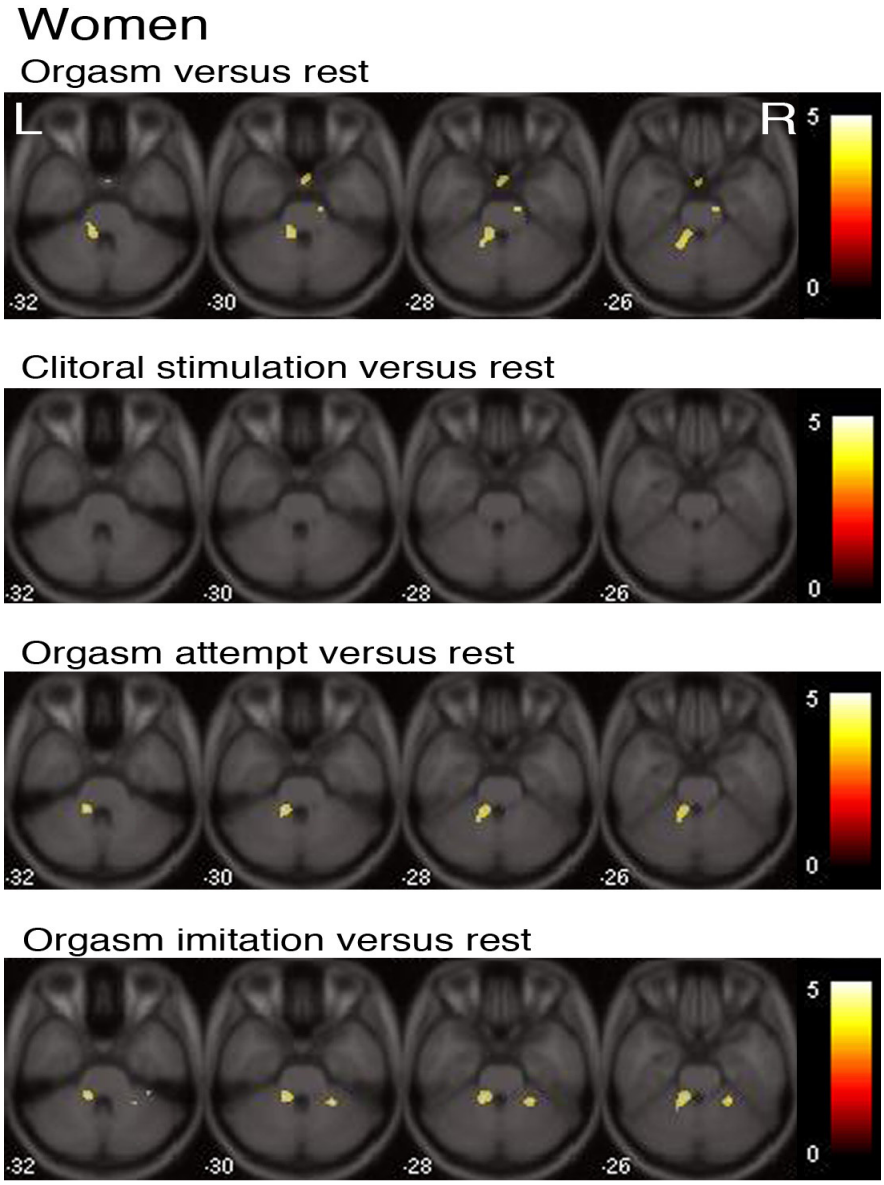

Figure 5. ***Axial plane sections (z=-32 to z=-26) of the brain in women showing the activated regions during real orgasm compared to rest (top).*** *This comparison resulted in activation in the left dorsolateral pontine tegmentum and right ventrolateral pontine tegmentum. The comparisons orgasm attempt and orgasm imitation versus rest (rows 3 and 4) also showed activation in the left dorsolateral pontine tegmentum, but not in the right ventrolateral pontine tegmentum. The comparison clitoral stimulation versus rest did not result in activation in any of these regions (second row).*

In females the activated area in the dorsolateral pontine tegmentum on the left side was also found in the comparison orgasm attempt versus rest i.e when women failed to reach orgasm during the time of the scan (Figure 5 row 3), or in the comparison imitation orgasm versus rest (Figure 5 bottom row), but not in the comparison clitoral stimulation versus rest (Figure 5 row 2), similar to the comparison penile stimulation versus rest (Figure 4 middle). Similar to men, in women the activated regions in the dorsolateral pontine tegmentum also extended into the cerebellar vermis, but only to a very limited extent. Notably, the activated area in the ventrolateral pontine tegmentum was only found in the comparisons ejaculation versus rest in men and orgasm versus rest in women (Figure 6), but not in any other comparison, neither in men nor in women.

In summary, the comparisons ejaculation versus rest in men and orgasm versus rest in women showed similar activation patterns in the pons, activation of the dorsolateral pontine tegmentum on the left side, and activation of the ventrolateral pontine tegmentum on the right side.

Discussion

The present results show that in humans, a region in the dorsolateral pontine tegmentum on the left side and another in the ventrolateral pontine tegmentum on the right side of the brain become activated during ejaculation in men or orgasm in women. This pattern of activation was much stronger in men, presumably reflecting the fact that in women the motor component of orgasm is weaker, shorter-lasting and less consistent than the motor component of male ejaculation (Bohlen et al., 1980; Bohlen et al., 1982; Carmichael et al., 1994; Kratochvil, 1994; Masters and Johnson, 1966). Importantly the activation in the ventrolateral pontine tegmentum was induced specifically by ejaculation in men or physical orgasm in women and not by associated sexual stimuli, nor in women who attempted but failed to reach orgasm or who imitated orgasm during the period of the scan by making voluntary movements of the pelvis.

Ejaculation is basically a form of voiding. Neuroimaging studies of another voiding activity, micturition, demonstrated in both men (Blok et al., 1997b) and in women (Blok et al., 1997a, 1998) that activation also occurred in the same region of the dorsolateral pontine tegmentum as seen in the present study. However during micturition activation was observed on the right and not on the left side. In figure 7 we show for comparison, a PET scan during micturition in women showing an almost identical area to that which occurs during ejaculation/orgasm, but with the activation on the right side. This

region activated during micturition corresponds with the pontine micturition centre (PMC) as identified in animal studies (Barrington, 1925; Holstege et al., 1986). The PMC contains neurons that project, via long descending pathways, to the parasympathetic motoneurons innervating pelvic organs and indirectly, via inhibitory neurons in the intermediomedial cell group to the pelvic floor somatic motoneurons in the sacral cord (Onuf's nucleus in humans) including those that innervate the external urethral sphincter, the external anal sphincter and the bulbo- and ischiocavernosus muscles (Mannen et al., 1977; Nagashima et al., 1979; Nakagawa, 1980; Petras and Cummings, 1978; Romanes, 1951; Schroder, 1980, 1981; Vanderhorst and Holstege, 1997).

It is clear that the projections to the detrusor and external urethral sphincter muscles are involved in micturition because bilateral lesions of the PMC resulted in a total retention of urine (Griffiths et al., 1990). However, the terminations of the PMC neurons on all parasympathetic motoneurons in the sacral cord, not simply on those that innervate the bladder, suggest that the PMC is also involved in controlling pelvic floor organs engaged in other functions than micturition. Our present findings in humans indicate that this control may extend to the muscular contractions associated with ejaculation. In the light of these findings the term PMC now seems inappropriate and we suggest a more accurate terminology would be the pelvic organ stimulating centre (POSC).

In the present study a second region located in the ventrolateral pontine tegmentum was activated during ejaculation in men or physical orgasm in women. Interestingly, a similar region in the ventrolateral pontine tegmentum was also activated during studies of micturition in humans. However this activation occurred only in participants who were unable to micturate when inside the scanner (around 50% of the cohort) (Blok et al., 1998; Blok et al., 1997b). These individuals, who found the experimental environment emotionally disturbing experienced involuntary "emotional" contractions of the pelvic floor, which may have contributed to their inability to urinate. Importantly, in the absence of micturition, no activation was found in the area of the dorsolateral pontine tegmentum. In contrast in participants who micturated successfully the reverse was true i.e activation in the dorsolateral but not in the ventrolateral pontine tegmentum (Figure 7) (Blok et al., 1997a, 1998; Blok et al., 1997b).

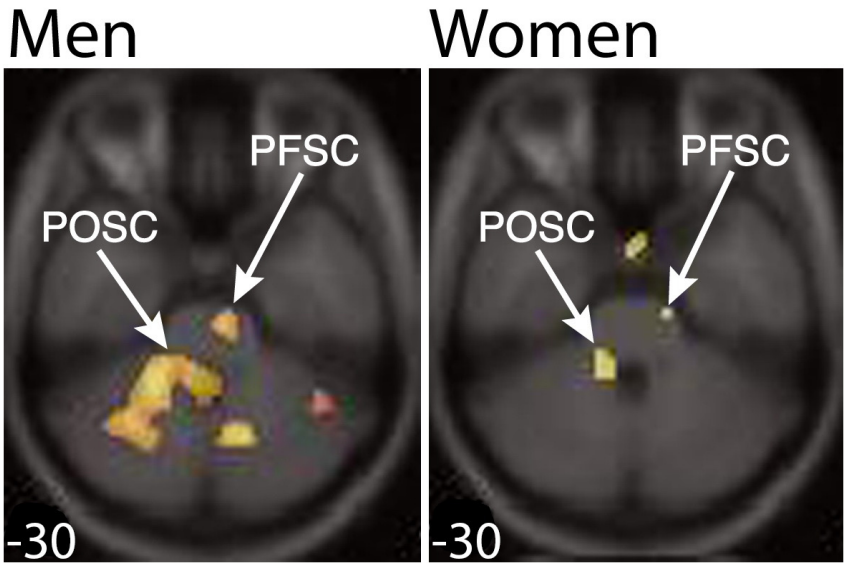

Figure 6. *Axial plane z=-30. On the left: the activated region in the left dorsolateral pontine tegmentum in men corresponds with the location of the pelvic organ stimulated center (POSC). In women the same but more limited activated region is present in the dorsolateral pontine tegmentum also on the left side. In both men and women another activated region is found in the ventrolateral pontine tegmentum on the right side, representing the pelvic floor stimulating center (PFSC).*

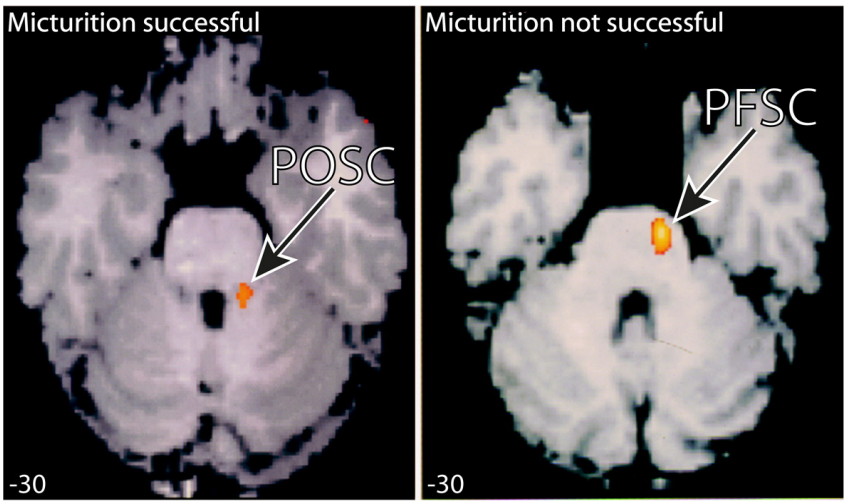

Figure 7. *In a previous PET-scan study in women (Blok et al. 1998) increased activation was shown in the POSC area during micturition (right side), while in those participants that kept their bladder sphincter closed for emotional reasons the PFSC was activated (right side). A similar activation pattern was found in men (Blok et al. 1997a).*

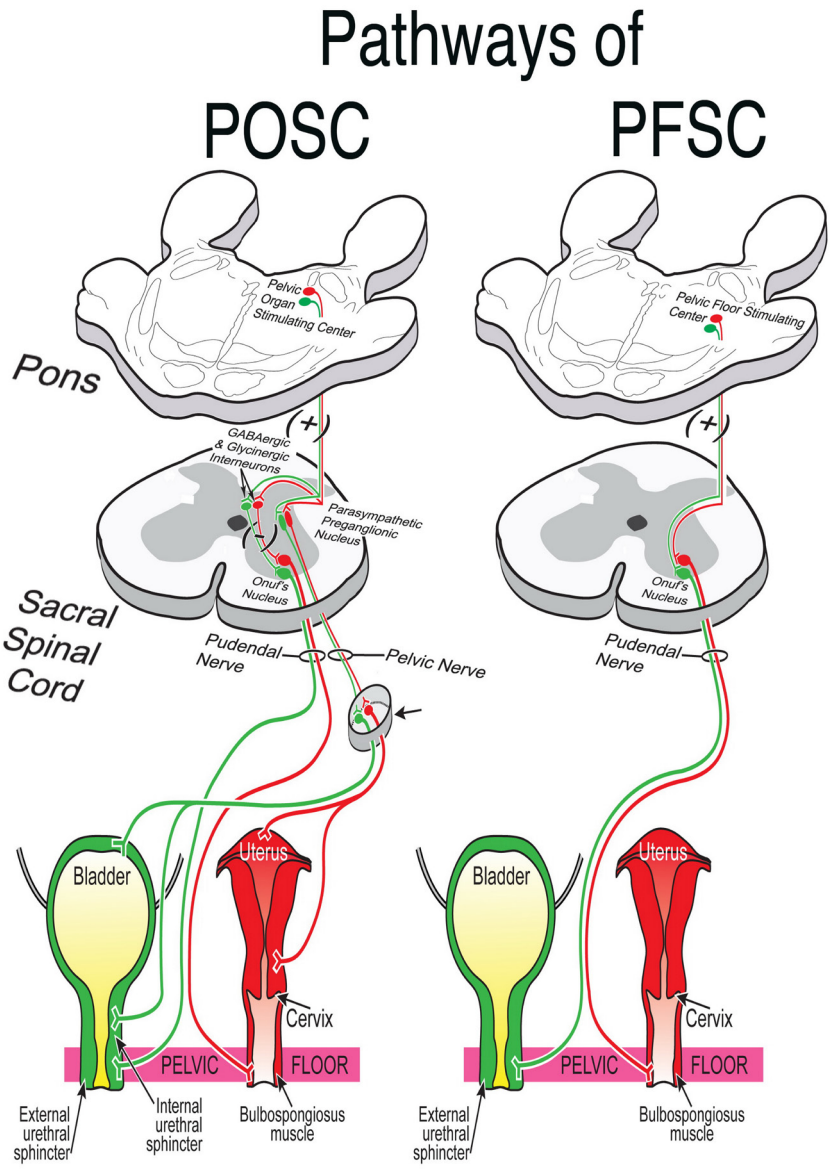

Figure 8. ***Summary diagram showing on the left the projections of the pelvic organ stimulating center (POSC).*** *On the right a parallel pathway exists from the pontine pelvic floor stimulating center (PFSC). The POSC has direct access via long descending pathways to the parasympathetic motoneurons in the sacral spinal cord innervating the pelvic organs as bladder and uterus. The PFSC projects directly to the nucleus of Onuf, which contains the motoneurons innervating the striated muscles of the pelvic floor including the ischio- and bulbocavernosus muscles as well as the external urethral and anal sphincters.*

Holstege and co-workers (Holstege and Kuypers, 1982; Holstege et al., 1979) have demonstrated in the cat that the lateral pontine tegmentum, which they termed the L-region (L = lateral), sends bilateral projections direct to Onuf's nucleus in the sacral cord. Electrical stimulation in this region, resulted in strong contractions of the entire pelvic floor (Holstege et al., 1986), not just the external urethral sphincter. Importantly the stimulation had no effect on the bladder detrusor muscle. Thus this projection does not appear to be specific for micturition but may be involved in storage of urine. Indeed, bilateral lesions of the L-region resulted in a complete incontinence for urine (Griffiths et al., 1990). In the present study this lateral region was also activated during ejaculation in men and during physical orgasm in women and presumably reflects the involvement of pelvic floor muscles in these events. Given its involvement in ejaculation and physical orgasm as well as in micturition, we propose the L-region should be re-named the pelvic floor stimulating center (PFSC).

A striking observation in both men and women was the laterality of activation in the pons during ejaculation/orgasm. Activation was detected in the POSC only on the left side of the brain. This was initially unexpected, given the bilateral nature of projections from the POSC region to the spinal cord (Holstege and Kuypers, 1982; Holstege et al., 1979). Interestingly, the opposite pattern of activation was observed during micturition, when activation of the POSC was present only on the right side (Blok et al., 1998; Blok et al., 1997b) (see also Fig 7 this chapter). Although still a contentious issue, there is evidence for laterality in forebrain processing of emotion (Miller et al., 2013). Whilst ejaculation and micturition are essentially voiding activities, arguably the former is associated with a much higher level of emotional arousal. At forebrain levels ejaculation was associated with right-sided activation whilst widespread de-activation was present on the left, an effect which was more pronounced in men than in women (Holstege and Huynh, 2011). The left sided activation in the POSC associated with ejaculation seen in the present study may be a reflection of this laterality in forebrain processing. Similarly, the left sided cerebellar activation seen during ejaculation in men may reflect laterality in its involvement in emotional processing (Schutter and van Honk, 2005; Strick et al., 2009).

Human sexual behavior is a complex interaction between biological events and culture mores thatt requires a strong interaction with higher-order brain systems (Georgiadis and Kringelbach, 2012; Georgiadis et al., 2012; Salu, 2011). Whilst ejaculation itself is essentially a physiological voiding function in males, sexual arousal in humans, which may ultimately lead to ejaculation is dependent on a host of factors such as social environment, social mores, anxiety levels, previous experience, guilt etc. This is reflected by the complex pattern of activation and deactivation of cortical and other forebrain structures that occurs during ejaculation in man (Georgiadis et al.,

2006; Georgiadis and Kringelbach, 2012; Georgiadis et al., 2012; Holstege, 2005a; Holstege et al., 2003). The POSC receives direct afferent input from the preoptic area (Holstege, 1987, 1991; Kuipers et al., 2006), a region shown to play an important role in ejaculation in animals (Malsbury, 1971; Robinson and Mishkin, 1966; Shimura et al., 1994; Vaughan and Fisher, 1962). Micturition too is another voiding function that is subject to complex forebrain processing associated with decision making in a social context e.g. whether the individual is in a safe and socially acceptable place to empty the bladder. The POSC also receives strong projections form the PAG, which appears to act as a neuronal "switch" that determines whether or not voiding of the bladder is permitted to occur (Blok and Holstege, 1994). The pontine nuclei POSC and PFSC may act as the final output to the spinal cord, which transmits information to the spinal relays to initiate the motor activity that mediates these voiding functions.

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Chapter 6

Discussion

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"In fear, the brain starves the heart of its bravest blood" - Rob Kall

One of the most important tools to accomplish survival of individual and species 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 corticobulbospinal 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, and also sexual behavior. The PAG, in turn, is under major influence of limbic system regions, such as amygdala, bed nucleus of the stria terminalis, hypothalamus, preoptic region, especially in humans, by various regions in the prefrontal and orbitofrontal cortex (Figure 1) (Holstege, 1991; Holstege and Huynh, 2013).

Motor control of ejaculation/orgasm

While the orgasm is undeniably one of the most delightful sensations known to mankind, similar to the feelings of reward in rats (Pfaus et al., 2001), little is known about the underlying physiological mechanisms controlling orgasmic responses. Orgasm consists of a chain of peripheral physical events, including contraction of sexual organs (uterine glands, uterus and vagina in females and contraction of ducts, and glands in males), as well as release of pressure by the external urethral sphincter. However, orgasmic sensations without input from genitals or without ejaculation have also been known (Newman et al., 1982).

Muscles in the pelvic area are controlled by the somatic and emotional motor systems. The emotional motor system uses the sympathetic hypogastric nerve, the parasympathetic pelvic nerve, and the somatic pudendal nerve. The pudendal nerve is also used by the somatic motor system. These nerves cooperate to activate the sexual arousal process to cause ejaculation and orgasm. Ejaculation consists of two main phases: emission and expulsion (Giuliano et al., 1995; Janig and McLachlan, 1987). During the emission phase, spermatozoa are mixed with fluids secreted by prostate glands, epididymis and seminal vesicles into the posterior urethra by chronological epithelial secretion and smooth muscle contractions. Lesions of the hypogastric plexus (sympathetic system) can cause failure of this seminal emission phase (Brindley et al., 1989). During the emission phase, a combined sympathetic and parasympathetic activation takes place. During the expulsion phase, the striated muscles of the external urethral sphincter produce the expulsion of sperm from urethra into the glans meatus (Giuliano and Clement, 2005). The expulsion phase is a spinal cord reflex as the ejaculatory process reaches a 'point of no return'.

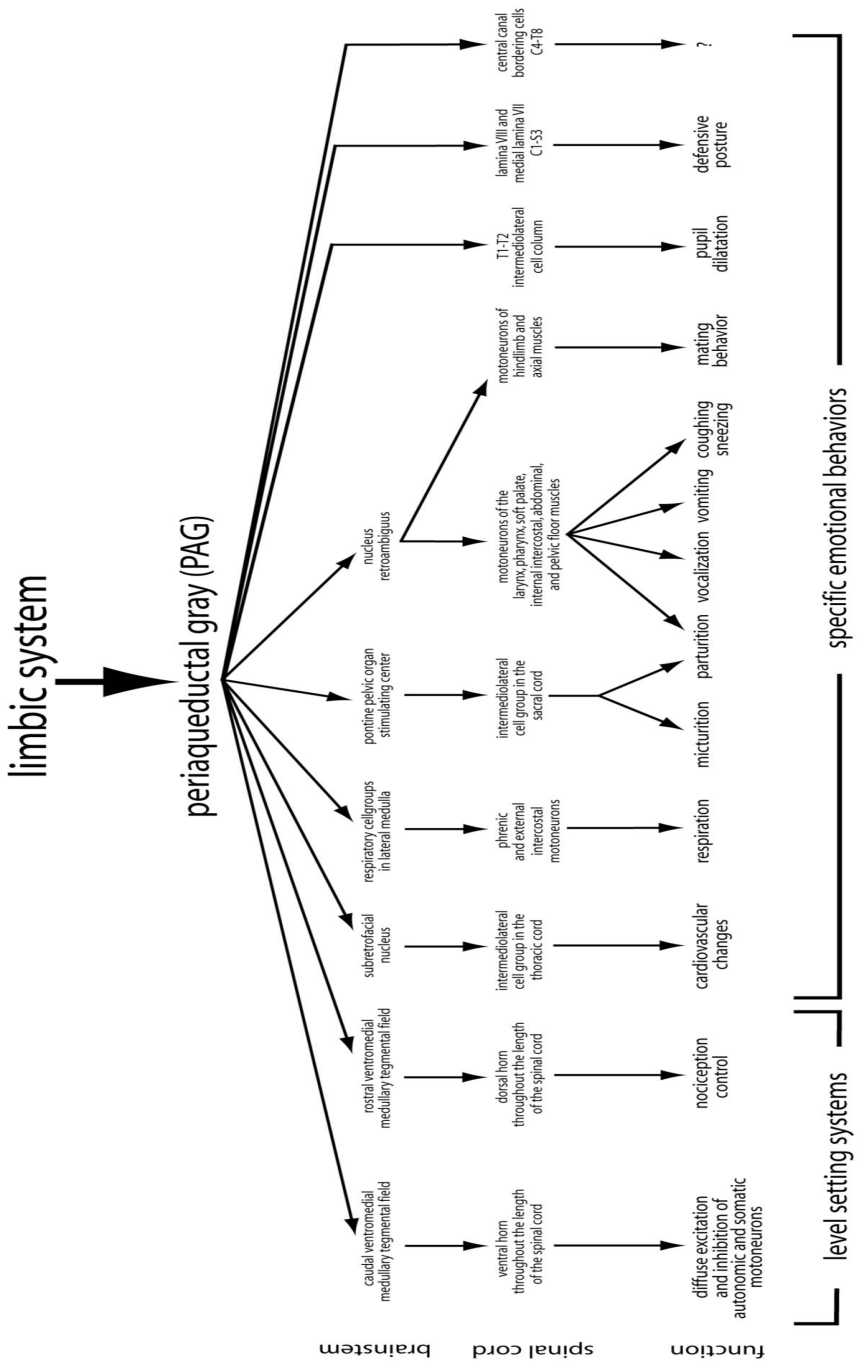


Figure 1. ***Summary diagram of the motor systems controlled by the periaqueductal gray (PAG).***

During this point, relaxation of external urethral sphincter and contraction of smooth muscle of the bladder neck prevents the backward flow of semen into the bladder; the pelvic floor muscles bulbospongiosus and ischiocavernosus rhythmically contract to push semen distally throughout the bulbar and penile urethra (Bettocchi et al., 2008; Gerstenberg et al., 1990). Although pelvic floor muscles are striated skeletal, their rhythmic contractions during the expulsion phase are triggered by the presence of semen in the bulbous urethra, not by voluntary control (McKenna et al., 1991). According to our new findings (Huynh et al., 2013), during the expulsion phase, the pelvic floor stimulating center (PFSC), receiving information from the urethra through the pelvic organ spinal relay center (POSRC) in the sacral cord and the PAG, excites the motoneurons in the nucleus of Onuf that innervate the pelvic floor.

Visual pathway in sexuality

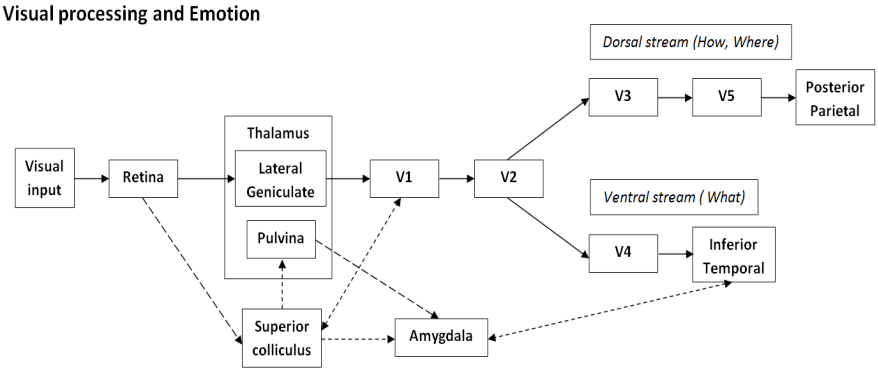
Vision is our dominant sense: it is estimated that 70% of all the sensory receptors in the body are in the eyes and that nearly half of the cerebral cortex is involved in some aspect of processing of visual information (Marieb, 1998).

Imaging studies on the brain responses to sexual stimuli, showed increased activation in many similar brain regions such as the anterior cingulate, medial prefrontal cortex, orbital prefrontal cortex, insula, amygdala, thalamus, and ventral striatum in both men and women (Canli and Gabrieli, 2004; Hamann et al., 2004; Karama et al., 2002; Ponseti et al., 2006). However, only men showed increased activation in the hypothalamus during the presentation of sexual stimuli, and its activation correlated significantly with the men's subjective reports of arousal (Stoleru et al., 1999). A study of Hamann (Hamann et al., 2004), using fMRI and still pictures, found a similar sex difference in hypothalamic activation in response to sexually explicit images of heterosexual activities and men also showed a higher general activation in response to sexual stimuli than women in the amygdala, even though men and women did not report different subjective levels of arousal to the photos. Other behavior experimental studies support the idea that men generally respond stronger to sexual stimuli than women (Laan et al., 1994; Money and Ehrhardt, 1972; Murnen, 1997; Schmidt, 1975; Steinman et al., 1981).

On the other hand, Tsujimura et al. found no statistically significant differences between men and women in viewing patterns in a sexual video showing heterosexual intercourse and speculated that men and women

might have similar visual attention patterns if the sexual stimuli were sufficiently explicit (Tsujimura et al., 2006; Tsujimura et al., 2009).

In the past, using visual sexual stimulation, only few authors showed some small deactivations of the visual cortex, and only in men using PET scan imaging (Bocher et al., 2001; Miyagawa et al., 2007; Mouras et al., 2003; Stoleru et al., 2003; Tsujimura et al., 2006). In 1995, Kawashima et al (Kawashima et al., 1995) proposed the "mind's eye" after finding a significant decrease in the regional cerebral blood flow in the visual cortex, which occurred irrespective of whether subjects had to close their eyes or were instructed to keep their eyes open when concentrating on cognitively demanding tasks.



Using eye-tracking study in men and women, Rupp and Wallen (Rupp and Wallen, 2007) showed that men and women exhibited different neural, genital, and subjective arousal responses to visual sexual stimuli and the menstrual cycle phase did not affect women's watching patterns. Lykins et al (Lykins et al., 2008) showed that the erotic and non-erotic information was visually processed in a different manner by both men and women. While men looked at opposite sex figures significantly longer than women did, women looked at same sex figures significantly longer than men did.

Within-sex analyses suggested that men had a strong visual attention preference for opposite sex figures as compared to same sex figures, whereas women appeared to disperse their attention evenly between opposite and same sex figures. These differences, however, were not limited to erotic images but evidenced in non-erotic images as well. For the brain itself, women have larger connections and more frequent interaction between their brain's left and right hemispheres. This accounts for women's ability to have better verbal skills and intuition. Men, on the other hand, have greater brain hemisphere separation, which explains their skills for abstract reasoning and visual-spatial intelligence.

Orgasmic hormones from pituitary

What is the role of female orgasm? This question remains controversial, but many studies suggest that women are more likely to reach orgasm during ovulation and fertility. When orgasm expands a woman's uterus, ejaculation has a higher chance to produce pregnancy. According to many sexualogical records, women that want to become pregnant reach orgasm more easily.

Oxytocin release

In all likelihood, the activation of the pituitary reflects an increase of the release of oxytocin and prolactin, since the plasma concentrations of these hormones are increased after sexual orgasm (Blaicher et al., 1999; Brody and Kruger, 2006; Carmichael et al., 1987; Carmichael et al., 1994; Exton et al., 1999; Exton et al., 2001; Kruger et al., 2003).

Oxytocin plays an important role in sexual function in mammals, including humans (Carmichael et al., 1987). Oxytocin plasma levels correspond with the strength of the lordosis response in rats as well as with the intensity of muscular contractions during orgasm in men and women (Pedersen and Boccia, 2002, 2006; Sansone and Komisaruk, 2001).

Exogenous oxytocin exposure may enhance arousal as well. Intranasal administration of synthetic oxytocin has shown to increase oxytocin in plasma levels in humans (Sayani and Chien, 1996). In 10 healthy males, exogenous intranasal oxytocin also increased sexual arousal during masturbation or during watching erotic movies (Burri et al., 2008). In a male patient, suffering from social avoidance and relational problems, intranasal oxytocin had a positive impact on libido, erection, and orgasm as well as on social tolerance (Macdonald and Feifel, 2012). In a twenty-six year old woman, intranasal oxytocin was used to help breast feeding, vaginal lubrication and vaginal contraction to improve sexual pleasure (Anderson-Hunt and Dennerstein, 1994).

Although sexual therapeutic oxytocin has been reported in men more than in women and increased levels of oxytocin during orgasm have been reported in both men and women, male ejaculation produces much lower increases of plasma oxytocin levels than female orgasm (around 2.5 pg/ml – baseline 1.8 pg/ml in men versus 4.5 pg/ml – baseline 2.5 pg/ml in women) (Carmichael et al., 1987), which explains why we did not find any pituitary activation in men comparing ejaculation with rest. It supports the concept that oxytocin plays an important role in sexual behavior (Donner and Neumann, 2009; Murphy et al., 1987). This concept is further supported by our finding that failed orgasm (orgasm attempt) or faking (imitating) orgasm did not produce an increased activation of the pituitary.

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Chapter 7

Summary - Samenvatting - Tóm tắt

Summary

Neuroanatomy is concerned with the study of the anatomy and organization of the nervous system. Strongly connected to neuroanatomy, neurophysiology is a branch of physiology and neuroscience that focuses on the functioning of the different parts of the nervous system. In neurophysiology, various functional neuroimaging techniques can be used to measure (changes in) brain function, particularly by comparing scans under different conditions. By creating these conditions or tasks and by comparing the brain activity between conditions, the brain regions involved can be determined. The ability to study the living brain, both in healthy and patient volunteers, has revolutionized our understanding of the functional segregation of the brain.

The aim of this thesis is to improve our understanding of the neurophysiology of human sexuality by using functional neuroimaging, in particular Positron Emission Tomography (PET).

In chapter 1, a short introduction is given to neurophysiology of sexuality as well as PET imaging and the data analysis methods employed in this thesis.

In chapter 2, a more detailed description of the human brain activations during sexual stimulation, ejaculation and orgasm is given and linked to brain circuits involved in the mating behavior of cats. This represents, in very broad terms, our knowledge about sexuality through functional neuroimaging at the start of the thesis.

In chapter 3, the important finding of the deactivation of the visual cortex in women during high erotic movies, but not low erotic and neutral movies, is reported and discussed. The primary visual cortex, Brodmann's area (BA 17), plays a vital role in basic survival mechanisms in humans. We measured differences in regional cerebral blood flow (rCBF) in the primary visual cortex during watching neutral, low-intensity erotic, and high-intensity erotic film segments by PET scanning of the brains of 12 healthy heterosexual premenopausal women, aged 18–47. Watching high-intensity, but not low-intensity erotic movies compared to neutral movies resulted in strong de-activation of the primary (BA 17) and adjoining parts of the secondary visual cortex. The strong de-activation during watching high-intensity erotic film might represent compensation for the increased blood supply in the brain regions involved in sexual arousal, also because high-intensity erotic movies do not require precise scanning of the visual field, because the impact is clear to the observer.

Chapter 4 focusses on the pituitary gland. The pituitary gland, at the protrusion of the hypothalamus in the base of the brain, plays an important role in the regulation of body homeostasis by releasing fluctuating amounts

of hormones into the bloodstream. Despite fluctuations in pituitary hormonal production, neuroimaging studies have never been able to demonstrate changes in the activation level of the pituitary. We demonstrated for the first time that neuroimaging techniques could identify increases in pituitary activation. In 11 healthy women the pituitary was activated during real orgasm, but not during orgasm imitation, clitoris stimulation or failed orgasm, signifying a higher blood supply to the pituitary. Note that in females, the pituitary releases the hormones oxytocin and prolactin that induce vaginal and uterus movements, ovulation and enhance sperm and egg transport. In contrast to the finding in women, no pituitary activation was found in 11 healthy men during ejaculation, which corresponds with the fact that ejaculation causes a much lower increase of oxytocin and prolactin in plasma than orgasm in women.

In chapter 5, we turn our attention to the pons. The pons (meaning “bridge” in Latin) is the location of the pontine micturition center (PMC, also known as Barrington’s nucleus). Micturition, ejaculation and female orgasm all involve specifically coordinated contractions of the pelvic organs and pelvic floor. Unlike micturition, little is know about the pathways involved in ejaculation and female orgasm. Therefore, PET scanning of rCBF was performed in 11 healthy heterosexual right-handed men during ejaculation and 11 healthy heterosexual right-handed women during orgasm. Activation patterns were found in the left dorsolateral pontine tegmentum and the right ventrolateral pons in both men and women. In men the activated region in the left dorsolateral pons extended into the vermis of the cerebellum. In women orgasm imitation and attempt versus rest showed similar activation in the dorsolateral, but not in the ventrolateral pons. In a previous PET study of micturition in humans the same region in the dorsolateral pons, also known as the pontine micturition center (PMC), was activated, but on the right side. Since this cell group now appears to be involved in both micturition and sexual behavior, we proposed that it should be re-named as the pelvic organ stimulating center (POSC). The ventrolateral pons that we found to be activated in ejaculation and orgasm is also involved in micturition. However activation occurred only in participants that were unable to micturate during the scan and involuntarily kept their pelvic floor contracted. This suggests that the region in the ventrolateral pons is involved in pelvic floor contractions during micturition and orgasm, which we propose to name the pelvic floor stimulating center (PFSC). The POSC and PFSC may both act as the final brain output for muscle activity involved in micturition, ejaculation and orgasm.

Samenvatting

Dit proefschrift beschrijft het onderzoek naar een aantal aspecten van sexualiteit met behulp van een neuro-imaging techniek uit de nucleaire geneeskunde, te weten Positron Emissie Tomografie (PET).

Hoofdstuk 1 geeft een korte introductie van neurofysiologie van de seksualiteit alsook van PET beeldvorming en de data analyse methode gebruikt in dit proefschrift.

In hoofdstuk 2 wordt een meer gedetailleerde beschrijving gegeven van humane hersenactivaties tijdens sexuele stimulatie, ejaculatie en orgasme en gerelateerd aan hersencircuits betrokken in het paringsgedrag van katten. Dit weerspiegelt in brede zin onze kennis van sexualiteit door middel van beeldvorming bij aanvang van dit proefschrift.

Een belangrijke bevinding (hoofdstuk 3) van dit proefschrift is de de-activering (d.w.z. verlaging van de hersenactiviteit) van de visuele cortex bij vrouwen terwijl deze kijken naar expliciete erotische filmfragmenten, maar niet tijdens suggestieve (sensuele) erotische en neutrale filmfragmenten. De primaire visuele cortex, (Brodmanngebied, BA 17), speelt een belangrijke rol in basale overlevingsmechanismes in mensen. Om deze veranderingen in kaart te brengen hebben we de regionale cerebrale doorbloeding (regional cerebral blood flow: rCBF) in de primaire visuele cortex gemeten met PET terwijl de proefpersonen keken naar neutrale, suggestieve (lage – intensiteit) erotische, en expliciete (hoge – intensiteit) erotische filmfragmenten. In totaal hebben 12 gezonde heteroseksuele pre-menopauzale vrouwen, 18-47 jaar oud, deelgenomen. Uit ons onderzoek blijkt dat het bekijken van hoge – intensiteit erotische filmfragmenten, in vergelijking met neutrale films, resulteerde in sterke de-activering van de primaire (BA 17) en de aangrenzende delen van de secundaire visuele cortex. Dit effect werd niet gevonden bij de laag - intensiteit erotische films. Deze sterke de-activering bij het bekijken van de hoge – intensiteit erotische filmfragmenten kan een fysiologisch effect van de seksuele opwinding zijn of een compensatie voor een verhoogde bloedtoevoer naar hersenengebieden betrokken bij seksuele opwinding. Een alternatieve verklaring is dat de context zo evident is dat een uitgebreide verwerking van het beeld niet noodzakelijk is.

De hypofyse (hoofdstuk 4) speelt ook een belangrijke rol in basale overlevingsmechanismes in mensen door de productie en vrijgifte van wisselende hoeveelheden hormonen in het bloed, afhankelijk van stress en angstniveaus. Ondanks deze veranderingen in de hormonale productie van de hypofyse, hebben beeldvormingsstudies studies nooit een verandering in de doorbloeding de hypofyse aangetoond. Een PET studie die wij

hebben uitgevoerd, toont voor het eerst aan dat een toegenomen activiteit van de hypofyse, aangetoond kan worden met behulp van perfusie PET. Dit betrof een studie bij 11 gezonde vrouwen met metingen tijdens een echt orgasme, een orgasme imitatie, stimulatie van de clitoris of tijdens een geplande maar mislukte orgasme. Alleen tijdens een echt orgasme kon een verhoogde rCBF van de hypofyse gemeten worden. De hypofyse produceert de hormonen oxytocine and prolactine, die zorgen voor contracties in de vagina en de baarmoeder. Ook spelen deze hormonen een rol bij de ovulatie en stimuleren zij het transport van sperma en eicellen.

Een vergelijkbaar onderzoek werd uitgevoerd bij 11 gezonde mannen. Het bleek dat een activatie van de hypofyse niet gevonden kon worden bij mannen. Het is bekend dat ejaculatie bij mannen een veel kleinere toename van oxytocine en prolactine plasmaconcentratie geeft dan een orgasme bij vrouwen, hetgeen een mogelijke verklaring is voor de gevonden verschillen.

Mictie (urineren), evenals ejaculatie en vrouwelijke orgasme, hebben een specifiek gecoördineerd samentrekkingspatroon van de bekkenorganen en de bekkenbodem. In tegenstelling tot mictie is er weinig bekend van het neurale netwerk dat betrokken is bij ejaculatie en vrouwelijk orgasme. Daarom hebben we met PET in 11 gezonde heteroseksuele rechtshandige mannen en 11 gezonde heteroseksuele rechtshandige vrouwen de rCBF bepaald tijdens ejaculatie en orgasme (hoofdstuk 5). We vonden dat de linker dorsolaterale pontine tegmentum en de rechter ventrolaterale pons geactiveerd bleken bij zowel mannen als vrouwen. Bij mannen bleek de geactiveerde regio in de linker dorsolaterale pons uitgebreid naar de vermis van het cerebellum. In een eerdere PET studie naar mictie is gebleken dat dezelfde regio in de dorsolateral pons, de zogenoemde pontine micturition center (PMC), was geactiveerd aan de rechter zijde. Omdat uit onze resultaten blijkt dat de PMC ook betrokken is bij seksueel gedrag stellen we voor dit de pelvic organ stimulating center (POSC) te noemen. De ventrolaterale pons die in onze studie geactiveerd bleek tijdens ejaculatie en vrouwelijk orgasme wordt ook geactiveerd bij mictie, maar alleen in personen die moeite hadden met mictie tijdens de scan. Dit suggereert dat de ventrolaterale pons betrokken is bij contracties van het bekkenbodem tijdens mictie en orgasme en we stellen voor om dit gebied de pelvic floor stimulating center (PFSC) te noemen. De POSC en de PFSC fungeren waarschijnlijk samen als het laatste output voor spieractiviteit betrokken bij mictie, ejaculatie en orgasme.

Tóm tắt

Giải phẫu học thần kinh liên quan đến việc nghiên cứu về giải phẫu và tổ chức của hệ thần kinh. Liên quan chặt chẽ với giải phẫu học thần kinh, sinh lý học thần kinh là một nhánh của sinh lý học và khoa học thần kinh, tập trung vào hoạt động của các phần khác nhau của hệ thần kinh. Trong sinh lý học thần kinh, nhiều kỹ thuật chẩn đoán hình ảnh có thể được sử dụng để đo lường (sự thay đổi) chức năng của não, đặc biệt bằng cách so sánh ảnh chụp não ở các điều kiện khác nhau. Để xác định chức năng của các vùng não khác nhau, các nhà khoa học đã tạo ra những điều kiện hoặc nhiệm vụ để người tham gia thử nghiệm thực hiện và sau đó so sánh hoạt động của não trong các điều kiện khác nhau này. Khả năng nghiên cứu não sống, ở người khỏe mạnh và các bệnh nhân tình nguyện, đã đưa sự hiểu biết của chúng ta về chức năng của các vùng não lên một bước tiến mới.

Mục đích của luận án này là nâng cao hiểu biết của chúng ta về sinh lý học thần kinh trong hoạt động tình dục ở loài người bằng cách sử dụng các kỹ thuật chẩn đoán hình ảnh, đặc biệt là chụp cắt lớp phát xạ phản điện tử (PET).

Chương 1 là phần tổng quan về sinh lý học thần kinh của hoat động tình dục cũng như hình ảnh PET và các phương pháp phân tích dữ liệu sử dụng trong luận án này .

Chương 2 mô tả chi tiết hơn về hoạt động não bộ người khi có kích thích tình dục, xuất tinh và cực khoái, liên hệ đến mạch não điều khiển hành vi giao phối ở mèo. Điều này thể hiện lại những kiến thức của chúng tôi về tình dục thông qua hình ảnh chức năng thần kinh ở phần đầu của luận án.

Chương 3 báo cáo và thảo luận về quá trình giảm kích hoạt của vỏ não thị giác ở phụ nữ khi xem phim khiêu dâm cường độ cao, nhưng không phải phim khiêu dâm cường độ thấp và phim trung tính. Vùng thị giác chính ở vỏ não, vùng Brodmann 17 (BA 17), đóng một vai trò quan trọng trong cơ chế của sự sống còn cơ bản ở loài người. Chúng tôi đo lường sự khác biệt về lưu lượng máu não (rCBF) tại vùng thị giác chính ở vỏ não của 12 phụ nữ tiền mãn kinh, khỏe mạnh, ở độ tuổi từ 18-47, khi họ xem các đoạn phim trung tính, khiêu dâm cường độ thấp và khiêu dâm cường độ cao bằng phương pháp PET quét não bộ. Khi xem các đoạn phim khiêu dâm cường độ cao, xuất hiện sự giảm kích hoạt mạnh của vùng vỏ não thị giác chính và vùng thị giác thứ cấp. Sự giảm kích hoạt này có thể diễn giải bằng sự chia sẻ lưu lượng mạch máu đến các vùng vỏ não khác liên quan đến sự kích thích tình dục, cũng như vì khi xem phim khiêu dâm cường độ cao não bộ không yêu cầu thông tin quá chính xác từ trường thị giác do các tác động đã quá rõ ràng đối với người xem.

Chương 4 tập trung vào tuyến yên. Tuyến yên, tuyến nội tiết vùng dưới

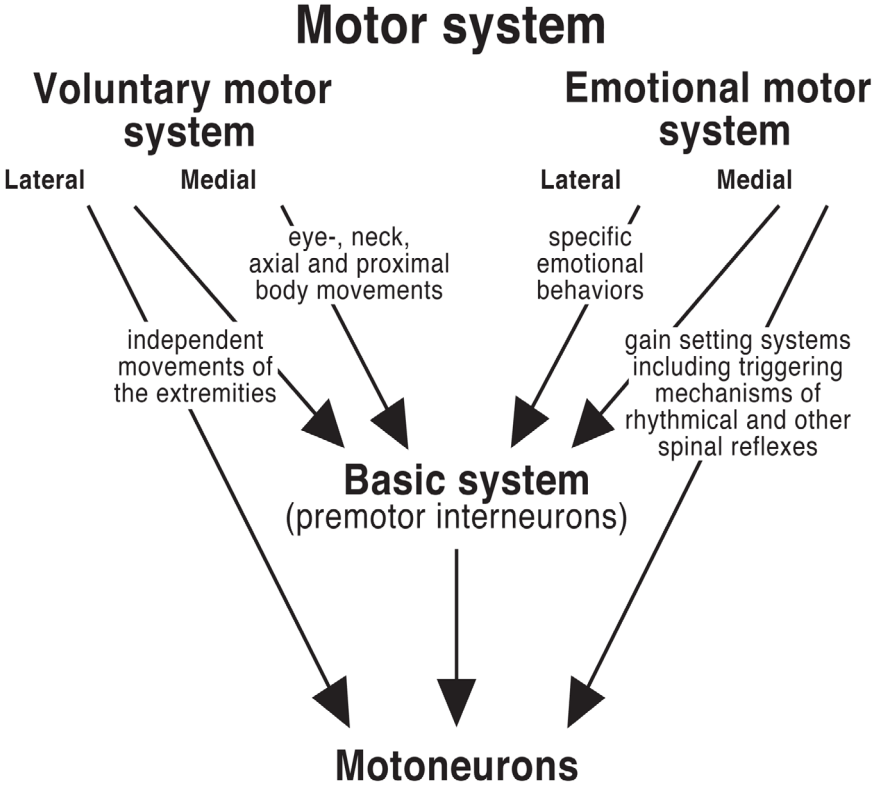
đồi có kích thước bằng hạt đậu, đóng một vai trò quan trọng trong việc điều hòa sự ổn định cơ thể bằng cách giải phóng các lượng khác nhau nội tiết tố vào máu. Mặc dù tuyến yên sản xuất nội tiết tố ở các mức độ khác nhau, các nghiên cứu chẩn đoán hình ảnh chưa bao giờ có thể chứng minh sự thay đổi trong mức độ kích hoạt của tuyến yên. Chúng tôi lần đầu tiên chứng minh với kỹ thuật chẩn đoán hình ảnh có thể xác định sự gia tăng kích hoạt tuyến yên. Ở 11 phụ nữ khỏe mạnh, tuyến yên đã được kích hoạt trong thời gian xảy ra cực khoái thật, nhưng không kích hoạt khi họ giả cực khoái, kích thích âm vật hoặc không đạt cực khoái, biểu hiện bằng sự tăng cung cấp máu đến tuyến yên. Cần lưu ý rằng ở phụ nữ, tuyến yên sản xuất ra các nội tiết tố oxytocin và prolactin để gây ra các co thắt âm đạo và tử cung, quá trình rụng trứng cũng như sự tăng cường khả năng vận chuyển trứng và tinh trùng để thụ tinh. Ngược lại, không thấy có sự kích hoạt tuyến yên nào ở 11 người đàn ông khỏe mạnh trong quá trình xuất tinh, tương ứng với thực tế là mức độ gia tăng oxytocin và prolactin trong huyết tương khi nam xuất tinh thấp hơn nhiều so với nữ khi đạt cực khoái.

Chương 5 tập trung tới cầu não. Cầu não (“cầu nối” trong tiếng Latin) có chứa trung tâm cầu não điều khiển tiểu tiện (PMC, còn được gọi là nhân Barrington). Tiểu tiện, xuất tinh cũng như cực khoái ở nữ đặc biệt liên quan đến sự phối hợp co thắt của các cơ quan và cơ ở vùng chậu. Không giống như tiểu tiện, có rất ít hiểu biết về các đường thần kinh điều khiển sự xuất tinh và cực khoái nữ. Vì vậy, chúng tôi đã thực hiện nghiên cứu quá trình xuất tinh ở 11 người đàn ông khỏe mạnh, dị tính, thuận tay phải, và quá trình đạt cực khoái ở 11 phụ nữ khỏe mạnh, dị tính, thuận tay phải bằng phương pháp chụp cắt lớp phát xạ phản điện tử (PET). Sự kích hoạt đã được tìm thấy ở phía trái lưng bên và phía phải bụng bên cầu não ở cả đàn ông và phụ nữ. Ở đàn ông, khu vực kích hoạt ở phía trái lưng bên cầu não mở rộng vào thùy nhộng của tiểu não. Ở phụ nữ, giả cực khoái và cố gắng đạt cực khoái cho thấy kích hoạt tương tự ở lưng bên nhưng không tác động tới bụng bên cầu não. Trong một nghiên cứu PET trước đó về quá trình tiểu tiện ở người, khu vực tương tự ở vùng lưng bên cầu não, còn được gọi là trung tâm cầu não điều khiển tiểu tiện (PMC), đã được kích hoạt nhưng chỉ ở phần phía bên phải. Vì nhóm tế bào này tham gia vào cả quá trình tiểu tiện và hành vi tình dục, chúng tôi đề xuất đổi tên thành trung tâm điều khiển các cơ quan vùng chậu (POSC). Vùng bụng bên cầu não mà chúng tôi phát hiện được kích hoạt trong khi xuất tinh và cực khoái cũng tham gia vào quá trình điều khiển tiểu tiện. Tuy nhiên sự kích hoạt chỉ xảy ra khi tình nguyện viên không đi tiểu trong quá trình chụp ảnh và vô tình làm co thắt vùng đáy chậu. Điều này cho thấy khu vực bụng bên cầu não có liên quan đến các cơn co thắt vùng chậu trong tiểu tiện và cực khoái, mà chúng tôi đề nghị đặt tên là trung tâm điều khiển đáy chậu (PFSC). Cả hai trung tâm POSC và PFSC có thể đóng vai trò là đầu ra cuối cùng của não bộ điều khiển hoạt động cơ bắp liên quan đến việc tiểu tiện, xuất tinh và cực khoái.

Chapter 8

Future perspectives

These studies have shown that sexual activity is, similar to micturition and defecation, an example of one of the lateral components of the so-called emotional motor system (Holstege, 1992, Holstege et al., 1996).



It means that this activity is not something magic, but totally controlled by the central nervous system, and especially by the brain and brainstem, because normal sexual performance is not possible in case of transection of the spinal cord at levels rostral to the sacral cord.

The findings presented in this thesis demonstrate that the same regions in the pontine tegmentum, i.e. the pelvic organ stimulating center (POSC) and the pelvic floor stimulating center (PFSC), that rule micturition also control ejaculation in men and real orgasm in women.

The next question is which brain regions control the POSC and PFSC. It is known that one of the most important regions that controls micturition (Blok and Holstege, 1994), and sexual activities (Mccarthy et al., 1991) is the periaqueductal gray (PAG). Interestingly another cell group that has direct access to the POSC is the preoptic region (Holstege, 1987). However nothing is known about which neurotransmitters play a role in these control

systems. Furthermore, the PAG, in turn, receives very strong afferents from major limbic regions as the amygdala (Hopkins and Holstege, 1978), bed nucleus of the stria terminalis (Holstege et al., 1985), hypothalamus (Holstege, 1987) and from the medial orbitofrontal cortex (Kuipers et al., 2006, An et al., 1998). These projections will play a crucial role in understanding the problems of many people concerning sexual behavior, for example hypoactive sexual desire disorder (HSDD), a disease which 10-15% of all women suffer from (Graziottin, 2007), and in all likelihood also many men (Derogatis et al., 2012).

Future studies have to find out which neurons have access to the POSC and PFSC, which neurotransmitters play a role in these connections and whether deep brain stimulation can play a role in those patients in which lesions in the above mentioned brain regions, including their efferent pathways, are the cause of problems with sexual activities. Finally it will turn out that sexual behavior as well as micturition can be manipulated as is the case with Parkinson disease (Little et al., 2013), pain problems (Bittar et al., 2005) and even depression (Mayberg et al., 2005).

The brain, which controls sexual behavior as well as all other motor activities, is a living computer, which needs to be maintained in good condition as long as possible. A patient whose brain proved to be still completely intact anatomically as well as functionally at this age of 115 years, demonstrated that this is very well possible (Den Dunnen et al., 2008).

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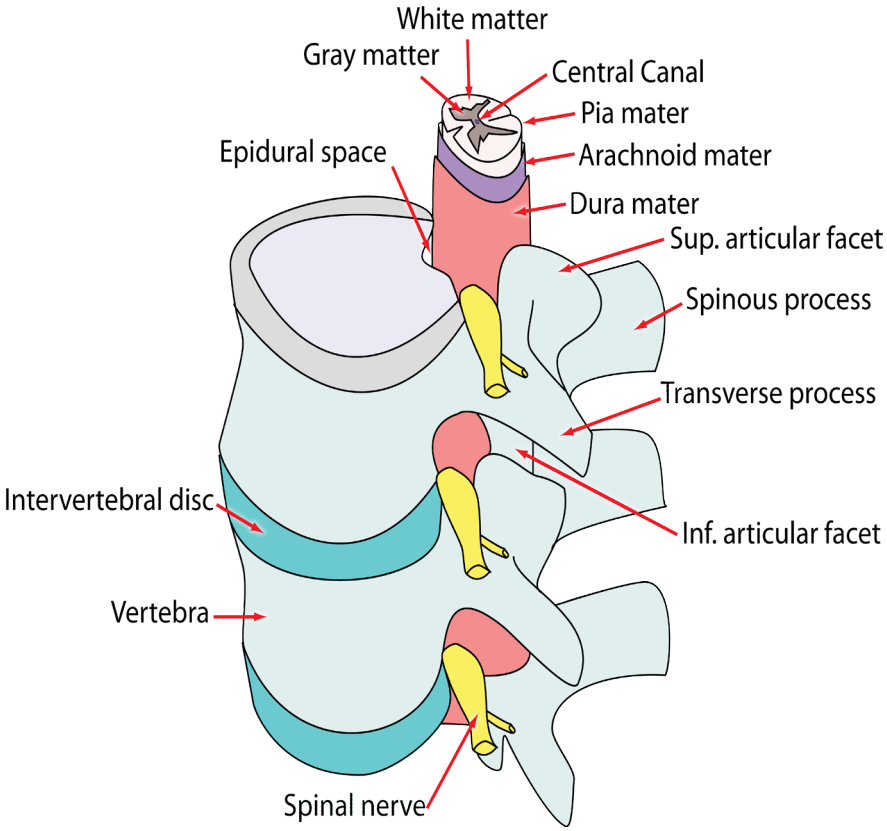
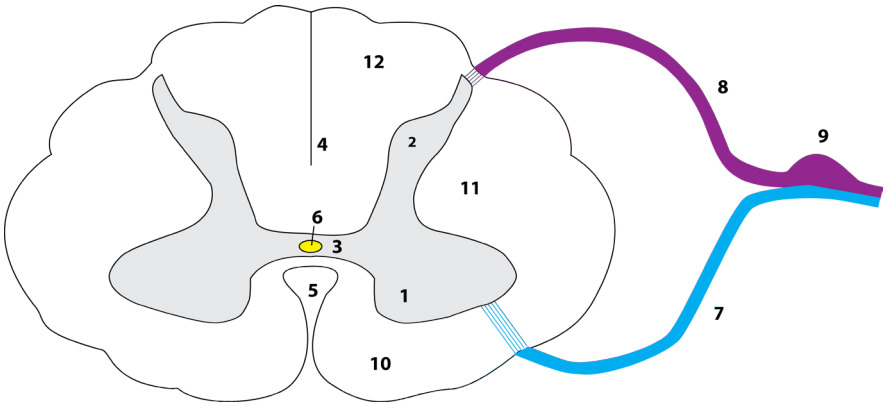


Extra figure 1A . ***The spinal cord and the vertebral column.***



Extra figure 1B. ***The axial section of the spinal cord.*** **Gray matter:** 1.Anterior horn 2.Posterior horn 3.Gray commissure **White matter:** 4.Posterior median fissure 5.Anterior median fissure 6.Central canal 7.Anterior root 8.Posterior root 9.Dorsal root ganglion 10.Anterior funiculus 11.Lateral funiculus 12.Posterior funiculus

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Curriculum Vitae

Hieu Kim Huynh (Huỳnh Kim Hiệu) was born on 5th October 1982 in Ho Chi Minh City, Vietnam. He studied medicine in Faculty of Medicine, University of Medicine and Pharmacy of Ho Chi Minh City from 2000-2006. From 2006-2007, he was trained as a spinal surgeon in the Hospital of Traumato-Orthopedics of Ho Chi Minh City under the supervision of Prof. Vo Van Thanh, a specialist on orthopedics and spinal cord surgery.

From 2007-2008, he received a grant of Agence universitaire de la Francophonie for the best medical students to study Master of medical devices in Faculty of Medicine and Pharmacy, University of Nantes, France. During this time in France, he had a pleasant inspiration of studying anatomy from Prof. Roger Robert, a specialist on neuroanatomy and neurosurgery especially on pudendal nerves.

From 2009-2012, he was a PhD student in Center for Uroneurology and in Nuclear Medicine and Molecular Imaging Department (NGMB) of Universitair Medisch Centrum Groningen (UMCG), the Netherlands. He had a good chance to complete this thesis under the gratifying and responsible supervision of Prof. Gert Holstege, Prof. Rudi Dierckx, and Dr.Antoon Willemsen. Prof. Gert Holstege is a specialist on neuroanatomy especially on periaqueduct gray, brainstem and spinal cord. Prof. Rudi Dierckx is a specialist in nuclear medicine and head of NGMB. Dr. Antoon Willemsen is an experienced medical physicist of NGMB.

During the time in Groningen, Hieu Kim Huynh met Hao Yen Tran, a beautiful Vietnamese PhD student; and finally he is married with her.