Brain Functional Imaging Studies Of Sexual Desire & Arousal In Human Males

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Preliminary draft

1. Why use brain functional imaging to study sexual desire and arousal (SDA)?

(a) Why study the brain to understand sexual desire and arousal?

The complex relationship between brain and mind has been the subject of philosophical and scientific debate for centuries. In our view, the brain is a two-way interface between mental mechanisms and peripheral physiological processes. In this sense, the brain plays a central role in psychophysiological processes. Viewing the brain as the interface between mental mechanisms and peripheral physiological processes does not necessarily imply any directional causality between brain and mind. Rather, what we see as mental and as peripheral physiological processes is conceived as two correlated aspects of the same unitary reality. This seems to be the view about soul and body that Spinoza proposed in Ethics.

According to recent sociobiological developments (reviewed in Rolls, 1999), the pressure of natural selection has led to the emergence of brain systems in which reward is associated with those sexual behaviors which increase fitness. Fitness is understood here as the aptitude to transmit one's genes to the next generation. Evolutionary pressure has thus selected the neurophysiological implementation of brain reward systems associated not only with copulation per se, but also with SDA and with sexual attraction to characteristics indicating a potential partner's fitness.

The central nervous system (CNS) plays a role at all successive stages of sexual behavior (Meisel and Sachs, 1994). Regarding the stage of processing of external stimuli, it has been shown in various mammals, in particular in monkeys, that hormonally determined characteristics of females, such as odor (Baum et al., 1977) and visual signals (Bielert, 1982) promote sexual behavior in males. These characteristics are evaluated through the central processing of sensory information. In humans also, sexual attraction is based on various factors (Buss, 1989) and the significance of these external stimuli as sexual incentives has to be assessed for the sexual response to develop. Although it has been hypothesized that the brain is involved in the assessment of such factors and of their potential reward value (Rolls, 1999), these brain mechanisms have not been systematically studied.

The cognitive aspects involved in further stages of SDA have been increasingly recognized in the literature. It has been proposed that human SDA cannot be defined adequately without highlighting the critical role of cognitive labeling and subjective experience in determining the response to a given stimulus as sexual (Rosen and Beck, 1988). Likewise, the concept of central arousal (Bancroft, 1989) refers to CNS activation and attentional factors that underlie the psychological processing of sexual stimuli.

Finally, at least in humans, SDA is also characterized by emotional responses and by motivational processes. The conscious perception of sexual desire belongs to the latter processes.

(b) Why use functional imaging to study the brain ?

Brain functional imaging techniques are currently the methods of choice to perform in vivo investigations of the cerebral physiological correlates of mental functions in human beings. Before the development of these techniques, studies of the cerebral basis of sexual motivation relied for a great part on animal models. In animals, the role played by subcortical structures in sexual behavior, in particular the septal nuclei, the amygdala, and hypothalamic nuclei (medial anterior preoptic area and ventromedial nucleus), has been well-documented (Meisel and Sachs, 1994). Knowledge from animal research is relevant to an understanding of some aspects of human sexuality. However, human sexual behavior has unique characteristics which distinguish it from the homologous behavior in other species. For instance, cognitive aspects of sexuality - such as sexual imagery - are likely to be much more important in humans than in any other species. Therefore, animal studies are notably insufficient to understand these specifically human aspects of sexual behavior and studies on human beings are needed to characterize the regions of the brain involved in the species-specific aspects of human sexual behavior.

The other source of knowledge on the brain basis of human SDA was the study of neurological patients, for instance those presenting epileptic seizures with sexual manifestations or those presenting sexual symptoms associated with focalized lesions. However important, those studies of pathological subjects were insufficient to describe the cerebral correlates of SDA in healthy individuals. A third group of studies has been based on post-mortem examinations of the brains, e.g., studies comparing specific hypothalamic nuclei in males with various sexual orientations.

The modern techniques of brain functional imaging have the great advantage of being minimally invasive, so that they may be performed in healthy volunteers. The most commonly utilized techniques have been Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI). The very first study was based on single photon emission tomography (SPECT), a technique with relatively low resolution. By contrast, a more recently introduced technique is magnetoencephalography (MEG), but to our knowledge its use to investigate sexual arousal is very preliminary. I shall focus here on PET and fMRI. Their spatial resolution allows to study brain areas at a macroscopic level, the spatial resolution being of the order of the millimeter. Their temporal resolution varies much, PET having a temporal resolution of the order of one minute, while the temporal resolution of fMRI is one- to two-seconds. Very briefly, PET allows to measure regional cerebral blood flow (rCBF). It is based on the administration of a small dose of a radioactive molecule – usually under the form of venous injection of $^{15}O-H_2O$ – that is carried to the brain by the bloodstream. The activity of brain areas is correlated to the local blood flow, which is itself correlated to the local radioactivity. Electrons from the tissue combine with positrons from the radioactive tracer to produce gamma rays (similar to x-rays). Special crystals, called photomultiplier-scintillator detectors, within the PET scanner detect the gamma rays. The camera records the millions of gamma rays being emitted, and a computer uses the information to generate 3-D pictures of the areas where radioactive substance has been present during the scan.

Functional MRI, as used in these studies, relies on the fact that the properties of the small bar magnets of water molecules in the brain change slightly between areas that are near blood with its oxygen exhausted relative to those near freshly oxygenated blood. The local increase in energy requirements arising as a consequence of neuronal firing is largely met through an increase in oxygen-based metabolism with the increased demand for oxygen being delivered seconds later by an increase in the local blood flow (the ***hemodynamic response***). Changes in the oxygenation level of the blood therefore occur as a consequence of neuronal activity and so the magnitude of change in signal intensity can be used as an indirect measure of excitatory input to neurons which is generally related closely to the cell firing rate. Thus, when there is a "blush" from increased activity, there is a small increase in signal intensity on the functional MRI scan (Parry and Matthews, 2002).

2. Studies selected for this review

In order to illuminate the patterns of activation and deactivation associated with sexual desire and sexual arousal, we searched peer-reviewed journals indexed in MEDLINE for manuscripts of PET and fMRI studies published between January, 1985, and June, 2003. This search led to the following list of 10 studies, presented in alphabetical order: Arnow et al.,, 2002; Beauregard et al.,, 2001 ; Bocher et al., 2000 ; Garavan et al., 2000 ; Karama et al., 2002 ; Mouras et al., submitted ; Park et al., 2001 ; Rauch et al., 1999 ; Redouté et al., 2000 ; Stoléru et al., 1999.

3. Review of Studies

(a) Samples

Sample sizes ranged from N=8 to N=14. Some studies have specified that subjects were heterosexual, while sexual orientation was left unspecified in others. No study has so far focused on homosexual men. Subjects were young; over the studies the age ranged from 18 to 42. Very few studies used biological assays to verify that subjects were physically healthy. Not verifying this point may be a problem, as we had to exclude a subject on the basis of abnormal prolactin plasma level and subjects may self-select themselves into the studies on the basis of doubts that they have about their sexual health. Such doubts that may turn out to be grounded in real disturbances. For instance, we have been struck by the high proportion of volunteers reporting a history of childhood phimosis, a problem that may have represented a psychological difficulty when these subjects were children and that may unconsciously have driven some of those adults to volunteer for the study.

(b) Techniques

Six studies have been based on fMRI and four on PET.

(c) Paradigms

In the majority of studies, subjects were instructed to simply watch the stimuli. In one study purporting to study the neural network associated with the ability to suppress SDA (Beauregard et al., 2000), in addition to the condition where subjects were requested to watch stimuli there was also a condition where subjects were asked to inhibit any emotional response. In one study, script-driven imagery was used (Rauch et al., 1999).

(d) Stimuli

Seven studies have used films, one has used films and photographs, one has used only photographs and finally one study was based on mental imagery. In functional imaging studies, what is measured is the increase – or the decrease – of regional brain activity in response to sexual stimuli as compared to a reference condition. The reference condition is based on the presentation of nonsexual stimuli. Almost all studies have used "emotionally neutral" stimuli. In addition, studies have used the presentation of visual stimuli representing nonsexual emotionally-laden scenes and/or social interaction, such as humor scenes, sports highlights, and a conversation between persons about drugs of abuse while smoking "crack cocaine". The latter film excerpt was used because in this study healthy subjects served as controls for an investigation of patients addicted to cocaine. Clearly, the expression "emotionally neutral" stimuli is a misnomer, as these stimuli are simply far less emotionally arousing than are sexual stimuli. However, they must still catch the subjects' attention to a sufficient degree so as not to be boring, which would induce an unwanted emotional state. It should also be noted that efforts have been made to control the emotional aspects of SDA, but less attempts have been devoted to control its motivational component. Progress remains to be made regarding the design and use of reference conditions that would induce nonsexual motivational states.

(e) Results

- <u>The occipitotemporal cortex</u>

Seven studies reported an activation in the associative visual areas that belong to the "ventral stream" of visual processing. Briefly, the ventral stream processes the information related to the content of the visual stimuli (the "what" aspect), while the dorsal stream, which involves parietal areas, processes the "where" aspect of visual stimuli. However, the activation of the occipitotemporal visual areas is probably not specific to the sexual nature of stimuli. As shown in a recent review (Phan et al., 2002), the majority of studies (60%) of visually induced emotional (nonsexual) states have reported an activation of the extrastriate occipital cortex and the visual stimuli that activated these areas were diverse, including pleasant and aversive pictures. These results suggest that the activation of the middle and inferior occipital gyri is not specifically related to the sexual condition used in the papers studied in the present review, but rather to the fact that visual sexual stimuli (VSS) are emotionally laden stimuli. Reiman et al. (1997) have suggested that these visual association areas could be involved in the evaluation procedure of complex visual stimuli with emotional relevance. It has also been proposed that the visual association areas are under the control of top-down influences, so that higher attention to VSS may have resulted in higher activity in visual association areas (Corbetta et al., 1993).

- The orbitofrontal cortex (OFC)

The OFC is that part of the frontal cortex that lies above the orbit of the eye. It is commonly partitioned into the lateral and the medial OFC. The OFC has been implicated as playing a major role in the assessment of the motivational relevance of stimuli (Rolls, 1999). This has been mainly established on the basis of studies in nonhuman primates and in human subjects. In our first study (Stoléru et al., 1999), we reported that the presentation of sexually stimulating film excerpts was associated with the activation of the right OFC. Importantly, it was the lateral part of the right OFC that was activated. Karama et al (2002) also found an activation in the lateral part of the right and the left OFC. In our second study (Redoute et al., 2000), we again found that the right OFC was activated, not only in response to films but also in response to sexually stimulating photographs. In this study, though the activation of the right OFC was not in the medial part of the OFC, its location was in a less lateral position than in our first study. While the distance from the sagittal plane was x=52 mm in the first study, it was 20 mm in the second. Importantly, this second study also showed a unique pattern of rCBF response in the right OFC, characterized by a maximum rCBF in the condition where moderately sexually arousing photographs were presented, with lesser activation recorded in the conditions where highly arousing photographs or films were presented. This meant that the activation of this area of the brain was not correlated to the level of SDA ***per se***. Moreover, in this region, rCBF in response to stimuli representing women was much higher than in response to other stimuli, i.e., documentary nature films and humor films where no women appeared. To which aspect(s) of stimuli was the activation of the right OFC related? In our study, on debriefing after PET sessions it is only for moderately sexually arousing photographs that subjects commented on the beauty of the presented women, reflecting the evaluation processes induced by this kind of stimuli. The activation of the OFC may be related to these evaluation processes rather than to SDA ***per se***. This interpretation was later corroborated by the findings of an fMRI study specifically targeted to the brain areas mediating the perception of facial attractiveness (Aharon et al., 2001), in which activation of the right OFC was related to perception of facial attractiveness. In another recent fMRI study on the neural correlates of facial attractiveness (O'Doherty et al., 2003), high attractiveness was again related to an activation in the OFC; however, the activation was located in the left medial OFC. The opposite contrast was also performed to detect areas with greater responses to low attractive faces relative to high attractive faces. Significant effects ($P < 0.05$, corrected for multiple comparisons) were evident in the right ventrolateral prefrontal cortex bordering right OFC.

Psychopathology may also raise additional questions on the functions of the OFC in sexual behavior. Burns and Swerdlow (2003) recently reported a case where a patient presented with acquired pedophilia and an inability to inhibit sexual urges despite preserved moral knowledge. The patient was found to have a right orbitofrontal tumor. This paper leads to questions regarding the role of the right OFC in the inhibition of sexual urges and in sexual orientation. It is important to note that this patient's tumor was very large so that information regarding the roles of the various parts of the right OFC cannot be derived from this paper.

- <u>The superior parietal lobule</u>

The superior parietal lobule is known to be involved in attentional processes. Not surprisingly, it has been shown to be activated in five of the reviewed studies.

· Neural network mediating motor imagery and motor preparation

As conceptualized by Decety and Grèzes (1999) from a cognitive neuroscience standpoint, motor imagery may be defined as a dynamic state during which the representation of a given motor act is internally rehearsed within working memory without any overt motor output. It has been proposed that such a simulation process corresponds to the conscious counterpart of many situations experienced in everyday life, such as watching somebody's action with the desire to imitate it, anticipating the effects of an action, preparing or intending to move, refraining from moving, and remembering an action. All of these tasks involve motor representations that recruit neural mechanisms specific to action planning. Planning of actions, preparing to move, simulating and observing actions can be regarded as having functional equivalence to the extent that they share these same motor representations and the same neural substrate. The motor representation comprises two parts: a representation of the body as a force-generator, and a representation of the goal of the action encoded in a pragmatic code. Many brain areas that we have found activated in response to VSS belong to the neural network mediating motor imagery. This is the case for the inferior parietal lobules, the left ventral premotor area, the anterior cingulate gyri, and the caudate nucleus.

The inferior parietal lobule has been found activated in five out of ten of the reviewed studies. The left inferior parietal lobule (Decety et al., 1994) or both inferior parietal lobules (Stephan et al., 1995) were activated by motor imagery tasks where subjects imagined they were performing movements with their right hand.

The left ventral premotor area was reported as activated in only one study (Redouté et al., 2000). However, it is important to note that in patients with hypoactive sexual desire disorder (HSDD) this region did not respond to VSS. As a result, when these patients were compared with healthy controls we found a statistically significant Group by Experimental Condition interaction in this brain area (Stoléru et al., in press). In interpreting this higher activation in healthy men, it is important to mention that motor imagery guided by an object in the visual field is associated with an activation in the ventral premotor area (Decety et al., 1994). This suggests that the actual presence of VSS in the environment may trigger the preparation of motor behavioral patterns.

One or both anterior cingulate gyri were reported as activated in seven of the reviewed studies. The anterior cingulate gyrus is an extended complex region that mediate several functions, including a role in cognitive, emotional, motivational and autonomic processes (Bush et al., 2000). One of the areas within the anterior cingulate gyrus, the caudal part, is particularly interesting here, as its role in motor function is known to be similar to the role of premotor and supplementary motor area cortices (Dum, 1993). This has led us to propose that the activation of the caudal part of the anterior cingulate gyri in response to the presentation of VSS may be one of the neural correlates of the preparation of motor behaviour associated with SDA (Redouté et al., 2000).

The caudate nuclei have been reported as activated in five papers. In order to interpret the activation of the caudate nucleus, it may be important to note that in the experimental paradigms used in these studies, no overt behavioral response was possible. Therefore, it is the premotor aspects of responses, as well as responses of regions concerned with withholding behavior, which were investigated. A recent model of basal ganglia function in motivated behavior (Rolls, 1999) is helpful to interpret the observed correlation between perceived sexual arousal and rCBF in the head of right caudate nucleus. According to this model, once the neurons in the orbitofrontal cortex have decoded the motivational significance of stimuli, it is essential that these reward-related signals should not be interfaced directly with motor behavior. Instead, what is required is that the signals enter an arbitration mechanism, which takes into account the cost of obtaining reward. It has been proposed that the basal ganglia participate in this function (Rolls, 1999). They receive inputs from numerous areas of the cerebral cortex, including the anterior cingulate gyrus which is strongly connected with the caudate nucleus and with the putamen. Cortical inputs compete within the caudate nucleus for behavioral output, and this nucleus maps each particular type of input to the appropriate behavioral output, implemented via the return basal ganglia connections to premotor/prefrontal cortex. This model is consistent with evidence from neuroimaging studies, i. e., (i) the activation of the putamen and/or the caudate nucleus in paradigms where the need for a motor response is conflicting with the need to withhold it (Pardo et al., 1990) and (ii) the activation of the head of the caudate nucleus upon volitional tic suppression in Tourette Syndrome (Peterson et al., 1998). Finally, the model is supported by clinical evidence, such as hypersexuality in patients with lesions circumscribed to the head of the caudate nuclei (Richfield et al., 1987). The above development strongly suggests that the model of the neural correlates of SDA should include a component consisting in the control of the motor expression of SDA. This would be consistent with the dual model of the control of sexual behavior proposed by Bancroft (Bancroft, 1999).

- The putamen

The putamen, which belongs to the basal ganglia, was found bilaterally activated in activated in three studies. Like the caudate nucleus, the putamen belongs to the striatum and has been shown to play a similar function as the caudate in withholding motor output. However, regarding the putamen, a study has suggested a possible relationship of its ventral part with the hedonic properties of the expected reward (Schultz et al., 1992). The putamen is also a region where electrical stimulation evoked most often an erection and/or genital manipulation in Macaca mulatta (Robinson and Mishkin, 1968). It is therefore interesting to point out that in the two studies which used penile plethysmography there was a linear correlation between regional cerebral blood flow or the BOLD signal in the putamens, one the one hand, and, on the other hand, the magnitude of penile tumescence (Arnow et al., 2002; Redouté et al., 2000).

· The insula

The activation of the insula has been one of the most consistent findings in neuroimaging studies of SDA (N=five studies reporting insular activation). The activation of this region has been shown to be associated with various emotional states, such as sadness, happiness, anger, fear, and disgust (Damasio et al., 2000; Phillips et al., 1997). Therefore, one of the possible interpretations of the activation of the insula may be that this region mediates the emotional component of SDA.

However, another interpretation should be considered. In a recent study on hypogonadal patients, we have found that compared with healthy controls the patients' right insula failed to get activated in response to VSS (Redouté et al., 2002). When patients were on hormonal replacement therapy, the response of the patients' right insula was no longer different from the response recorded in controls. Interestingly, two recent neuromorphological studies (Gerendai et al., 2000; .Lee et al., 2002) have allowed to trace a neural route between the central nervous system and the testes and to identify neurons involved in the innervation, and presumably in the control, of testicular secretion. In these studies, neurotropic virus was injected into the testis and virus-infected neurons were visualized by immunocytochemistry. Virus-labeled neurons could be demonstrated in various regions, including the periaqueductal grey matter, the hypothalamic paraventricular nucleus, the lateral hypothalamus, and also in telencephalic structures including the preoptic area, the bed nucleus of the stria terminalis, the central nucleus of the amygdala, the insula and the frontal cortex. In the insular cortex, intensive labeling was present and the infection was mainly restricted to pyramidal cells.

· The claustrum

The claustrum is a sheet of grey matter that lies beneath the insula from which it is separated by white matter. It is one of the most mysterious structures of the brain and its embryologic origin remains controversial. Its activation in response to

VSS has initially been a surprise. However, this finding was reported in three studies. The role of the claustrum in SDA is not clear. One proposed interpretation is that the claustrum mediates cross-modal transfer of visual input to imagined tactile stimulation (Arnow et al., 2002).

- The hypothalamus

In four studies, an activation of the hypothalamus was found associated with SDA. Interestingly, in two studies there was a linear correlation between the magnitude of penile tumescence as measured by plethysmography and the magnitude of the hypothalamic response as measured in PET or fMRI (Arnow et al., 2002; Redouté et al., 2000). Furthermore, we have reported a preliminary case study where the curve of the BOLD signal predicted the curve of the penile response observed 30 seconds after the BOLD signal. In other words, from a statistical standpoint the time lag for which the BOLD signal predicted most powerfully the penile response was 30 seconds (Stoléru et al., 2003).

- Deactivated temporal areas

Three studies have reported a deactivation of several areas belonging to the lateral temporal cortex. These areas were distinct from the areas of the temporooccipital cortex that were mentioned above as being activated in response to VSS. It is well known that the removal of temporal lobes is followed by dramatic hypersexuality (Klüver and Bucy, 1939). In addition, in a study where subjects were requested to actively attempt to inhibit the feeling of SDA in response to VSS, some temporal regions showed an activation (Beauregard et al., 2001). Together, these findings suggest that the alleviated inhibition from temporal lobes allows for the development of SDA. In other words, these temporal regions could exert a tonic, i.e., continuous, inhibition on the development of SDA, while the role of the basal ganglia would be to withhold the behavioral expression of an already current state of SDA.

(f) A proposed model of SDA in healthy men

Redouté et al. (2000) have proposed a four-component neurobehavioral model of the brain processes involved in SDA, comprising cognitive, motivational, emotional and autonomic components. In addition, each component is controlled by inhibitory processes. The cognitive component comprises (i) a process of appraisal through which stimuli are categorized as sexual incentives and quantitatively evaluated as such, (ii) increased attention to stimuli evaluated as sexual, and (iii) motor imagery in relation to sexual behavior. We have interpreted the activation of the right lateral orbitofrontal cortex, of the right and the left inferior temporal cortices, of the superior parietal lobules, and of areas belonging to the neural network mediating motor imagery (inferior parietal lobules, left ventral premotor area) as the neural correlates of this cognitive component of the model (Stoléru et al., in press). The process of appraisal is postulated as being the earliest one, with other processes depending on it. Thus, cognitive appraisal of stimuli as sexual is not considered as preceding SDA, but as the first step of the whole process of unfolding SDA. The emotional component includes the specific hedonic quality of SDA, i.e., the pleasure associated with rising arousal and with the perception of specific bodily changes, such as penile tumescence. We have interpreted the activation of the right insula as neural correlates of this emotional component. The motivational component comprises the processes that direct behavior to a sexual goal, including the perceived urge to express overt sexual behavior. We have suggested that the activated caudal part of the left anterior cingulate gyrus, as well as the right and left claustrum were neural correlates of this motivational component. The autonomic and endocrinological components include various responses (e.g., cardiovascular, respiratory, genital) leading the subject to a state of physiological readiness for sexual behavior. We have proposed that the activation of the rostral portion of the anterior cingulate gyrus, of the anterior part of the right insula and of the posterior hypothalamus participated in the mediation of the autonomic responses of SDA. These four components are conceived as closely interrelated and coordinated. For instance, the emotional component is partly based on the perception of bodily changes generated by the autonomic component. Finally, inhibitory processes comprise (i) processes that are active between periods of SDA and that prevent its emergence; we have suggested that this type of inhibitory control was exerted by regions of the temporal lobes where activity decreased in response to VSS; (ii) cognitive processes that may – at least in patients with decreased sexual desire – “devalue” the sexual relevance of VSS; we have proposed that this type of control was mediated by the medial orbitofrontal cortex (Stoléru et al., in press); and (iii) processes that control the overt behavioral expression of SDA, once SDA has begun to develop; we have proposed that the head of the right caudate nucleus and the putamen bilaterally participate in this function.

(g) Specificity of neural correlates of sexual arousal

Our results support the notion that SDA is a composite psychophysiological state correlated with the activation/deactivation of several brain regions. Among those regions, a majority, when considered individually, have been associated with other emotional or motivational states. For instance, the anterior cingulate gyrus and the claustrum have been activated in several affective states, including negatively valenced emotions (Benkelfat et al., 1995; Dougherty et al., 1999). Then, what is specific of the neuroanatomical correlates of SDA? This specificity may be related to: (i) a distinctive pattern of activated/deactivated areas and/or (ii) the activation/deactivation of discrete areas within the broad regions demonstrated by PET, e.g., the part of the rostral ACG reported to control erection in animals and the part of the somatosensory cortex related to the perception of penile tumescence; (iii) small regions where activation cannot be recorded reliably with current neuroimaging techniques.

(h) Methodological caveat

As noted by Canli and Amin (2002), It is important to keep in mind that when researchers identify a region as being active, they mean to say that the activation in that region during one condition (e.g., seeing a sad face) is signicantly greater than during a control condition (e.g., seeing a neutral face). What constitutes a significantly greater activation is, in a way, in the eye of the beholder. Quantitatively, that decision will be made through statistical analysis: activation in one condition will be called significantly greater than another, if a certain threshold of statistical certainty is crossed. Thus, lowering the threshold will create more regions that are statistically significant, whereas raising the threshold will reduce the number of significant regions. The choice of the threshold is largely determined by convention amongst researchers, rather than an absolute standard. Reporting a brain activation pattern is therefore primarily a statistical interpretation of a very complex dataset, and may be interpreted differently by different researchers.

(i) Clinical implications

We believe that in the long run the advances made in the pathophysiology of SDA will allow to make a corresponding progress in the treatment of disorders affecting sexual desire and SDA. However, it should be mentioned that the techniques that have been presented have not yet been proven to be useful as diagnostic tools at the level of the individual patient.

4. References

Aharon I, Etcoff N, Ariely D, Chabris CF, O'Connor E, Breiter HC. 2001 Beautiful faces have variable reward value: fMRI and behavioral evidence. Neuron 32:537-551.

Canli T, Amin Z. (2002). Neuroimaging of emotion and personality: scientific evidence and ethical considerations. Brain Cogn;50:414-431.

Arnow, B. A., Desmond, J. E., Banner, L. L., Glover, G. H., Solomon, A., Polan, M. L., Lue, T. F., and Atlas, S. W. 2002. Brain activation and sexual arousal in healthy, heterosexual males. ***Brain*** **125**: 1014-1023.

Bancroft J. 1989. Human sexuality and its problems. London: Churchill Livingstone. 748p.

Bancroft J. 1999. Central inhibition of sexual response in the male: a theoretical perspective. Neurosci Biobehav Rev 23:763-784.

Baum MJ, Everitt BJ, Herbert J, Keverne EB. 1977. Hormonal basis of proceptivity and receptivity in female primates. Arch Sex Behav 6:173-192.

Beauregard, M., Levesque, J., and Bourgouin, P. 2001. Neural correlates of conscious self-regulation of emotion. ***J. Neurosci.*** **21**: RC165.

Benkelfat C, Bradwejn J, Meyer E, Ellenbogen M, Milot S, Gjedde A, Evans A. 1995. Functional neuroanatomy of CCK4-induced anxiety in normal healthy volunteers. Am J Psychiatry 152:1180-1184.

Bielert C. 1982. Experimental examinations of baboon (Papio ursinus) sex stimuli. In: Snowdown CT, Brown CH & Petersen MR, editors. Primate Communication. London: Cambridge University Press, P373-395.

Bocher, M., Chisin, R., Parag, Y., Freedman, N., Meir Weil, Y., Lester, H., Mishani, E., and Bonne, O. 2001. Cerebral activation associated with sexual arousal in response to a pornographic clip: a 15O-H2O PET study in heterosexual men. ***NeuroImage*** **14**: 105-117.

Burns JM, Swerdlow RH. 2003 Right orbitofrontal tumor with pedophilia symptom and constructional apraxia sign. Arch Neurol. 60:437-440.

Bush G, Luu P, Posner MI 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci.;4:215-222.

Buss DM. 1989. Sex differences in human mate preferences: evolutionary hypotheses tested in 37 cultures. Behav Brain Sci 12:1-14.

Canli T, Amin Z. (2002). Neuroimaging of emotion and personality: scientific evidence and ethical considerations. Brain Cogn;50:414-431.

Corbetta, M., Miezin, F. M., Shulman, G. L., and Petersen, S.E. 1993. A PET study of visuospatial attention. ***J. Neurosci.*** **13**: 1202-1226.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., Hichwa, R.D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nature Neuroscience 3, 1049-1056.

Decety, J., 1996. The neurophysiological basis of motor imagery. Behavioural Brain Research 77, 45-52.

Decety, J., Grezes, J., 1999. Neural mechanisms subserving the perception of human actions. Trends in Cognitive Sciences 3, 172-178.

Decety, J., Perani, D., Jeannerod, M., Bettinardi, V., Tadary, B., Woods, R., Mazziotta, J., Fazio, F., 1994. Mapping motor representations with positron emission tomography. Nature 371, 600-602.

Dougherty DD, Shin LM, Alpert NM, Pitman RK, Orr SP, Lasko M, Macklin ML, Fischman AJ, Rauch SL. 1999. Anger in healthy men: a PET study using script-driven imagery. Biol Psychiatry 46:466-472.

Dum RP (1993): Cingulate motor areas. In: Vogt BA, Gabriel M, editors. Neurobiology of the cingulate cortex and limbic thalamus. Boston: Birkhäuser, p 415–441.

Garavan, H., Pankiewicz, J., Bloom, A., Cho, J. K., Sperry, L., Ross, T. J., Salmeron, B. J., Risinger, R., Kelley, D., and Stein, E. A. 2000. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. ***Am. J. Psychiatry*** **157**: 1789-1798.

Gerendai, I.E. Tóth, Z. Boldogkoi, I. Medveczky and B. Halász (2000) Central nervous system structures labeled from the testis using the transsynaptic viral tracing method. J. Neuroendocrinol. 12, 1087-1095.

Karama, S., Lecours, A. R., Leroux, J. M., Bourgouin, P., Beaudoin, G., Joubert, S., and Beauregard, M. 2002. Areas of brain activation in males and females during viewing of erotic film excerpts. ***Hum. Brain Mapp.*** **16**: 1-13.

Klüver H, Bucy PC. 1939. Preliminary analysis of functions of the temporal lobes in monkeys. Arch Neurol Psych 42:979-1000.

Lee, S., Miselis, R., Rivier C. (2002). Anatomical and functional evidence for a neural hypothalamic-testicular pathway that is independent of the pituitary. Endocrinology 143: 4447–4454.

Meisel RL, Sachs BD. 1994. The physiology of male sexual behavior. In: Knobil E & Neill JD, editors. The Physiology of Reproduction. New York: Raven Press, Vol. 2, pp 3-105.

Mouras H; Stoleru S; Bittoun J; Glutron D; Pelegrini-Issac M; Paradis A-L; and Burnod Y. Brain processing of visual sexual stimuli in healthy men: A functional magnetic resonance imaging study. Submitted.

O'Doherty J, Winston J, Critchley H, Perrett D, Burt DM, Dolan RJ. 2003 Beauty in a smile: the role of medial orbitofrontal cortex in facial attractiveness. Neuropsychologia;41:147-155.

Pardo JV, Pardo PJ, Janer KW, Raichle ME. 1990. The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proc Natl Acad Sci USA 87:256-259.

Park, K., Seo, J. J., Kang, H. K., Ryu, S. B., Kim, H. J., and Jeong, G. W. 2001. A new potential of blood oxygenation level dependent (BOLD) functional MRI for evaluating cerebral centers of penile erection. ***Int. J. Impot. Res.*** **13**: 73-81.

Parry, A, Matthews, P. M. 2002. Functional magnetic resonance imaging: a window into the brain. http://www.psy.vanderbilt.edu/faculty/blake/214_F2002/fMRI/fmri_intro.html, consulted in June, 2003.

Peterson BS, Skudlarski P, Anderson AW, Zhang H, Gatenby JC, Lacadie CM, Leckman JF, Gore JC. 1998. A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. Arch Gen Psychiatry 55:326-333.

Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, Bullmore ET, Perrett DI, Rowland D, Williams SC, Gray JA, David AS. 1997 A specific neural substrate for perceiving facial expressions of disgust. Nature;389:495-498.

Redoute J.; Stoleru S.; Costes N.; Lavenne F.; Pugeat M.; Le Bars D.; Cinotti L.; Dechaud H.; Pujol J.F.2002 Effects of testosterone on brain processing of visual sexual stimuli in normal and in hypogonadal men. Poster presented at the 32rd annual meeting of the Society for Neuroscience, Orlando, November 2002.

Redouté, J., Stoléru, S., Grégoire, M. C., Costes, N., Cinotti, L., Lavenne, F., Le Bars, D., Forest, M. G., and Pujol, J. F. 2000. Brain processing of visual sexual stimuli in human males. ***Hum. Brain Mapp.*** **11**: 162-177.

Reiman, E. M., Lane, R. D., Ahern, G. L., Schwartz, G. E., Davidson, R. J., Friston, K. J., Yun, L. S., and Chen, K. Neuroanatomical correlates of externally and internally generated human emotion. ***Am. J. Psychiatry*** **154**: 918-925.

Richfield EK, Twyman R, Berent S. 1987. Neurological syndrome following bilateral damage to the head of the caudate nuclei. Ann Neurol 22:768-771.

Robinson BW, Mishkin M. 1968. Penile erection evoked from forebrain structures in Macaca mulatta. Arch Neurol 19:184-198.

Rolls ET. 1999. The brain and emotion. New York: Oxford University Press. 367p.

Rosen RC, Beck JG. 1988. Patterns of sexual response. In: Rosen RC & Beck JG, editors. Patterns of sexual arousal. Psychophysiological processes and clinical applications. New York: Guilford, pp 23-52.

Schultz W, Apicella P, Scarnati E, Ljungberg T. 1992. Neuronal activity in monkey ventral striatum related to the expectation of reward. J Neurosci 12:4595-4610.

Stephan, K.M., Fink, G.R., Passingham, R.E., Silbersweig, D., Ceballos-Baumann, A.O., Frith, C.D., Frackowiak, R.S., 1995. Functional anatomy of the mental representation of upper extremity movements in healthy subjects. Journal of Neurophysiology 73, 373-386.

Stoléru, S., Grégoire, M. C., Gérard, D., Decety, J., Lafarge, E., Cinotti, L., Lavenne, F., Le Bars, D., Vernet-Maury, E., Rada, H., Collet, C., Mazoyer, B., Forest, M. G., Magnin, F., Spira, A., and Comar, D. 1999. Neuroanatomical correlates of visually evoked sexual arousal in human males. ***Arch. Sex. Behav.*** **28**: 1-21.

Stoléru, S., Redouté, J., Costes, N., Lavenne, F., Le Bars, D., Dechaud, H., Forest, M. G., Pugeat, M., Cinotti, L., And Pujol J.-F. (in press) Brain Processing of Visual Sexual Stimuli in Men with Hypoactive Sexual Desire Disorder. Psychiatry Research : Neuroimaging.

Stoléru S, Mouras H, Rouxel R, Pélégrini-Issac M, Grandjean B, Glutron D, Bittoun J, Burnod Y. 2003. Neuroanatomical correlates of penile tumescence recorded through volumetric phallometry in an fMRI environment [abstract]. Presented at the Ninth International Conference on Functional Mapping of the Human Brain, June 19-22, 2003, New York, NY. Available on CD-Rom in NeuroImage, Vol. 19, No. 2.

Tiihonen, J., Kuikka, J., Kupila, J., Partanen, K., Vainio, P., Airaksinen, J., Eronen, M., Hallikainen, T., Paanila, J., Kinnunen, I., and Huttunen, J. (1994). Increase in cerebral blood flow of right prefrontal cortex in man during orgasm. ***Neurosci***. ***Lett.*** 170: 241-243.