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Current neurobiological sciences allow emerging from the narrow margin of approach that asks if the homosexual person “is born or is made? The brain of all human being is born and is made. As in all that is human, the first level is biological and this intrinsically unites with the level of interpersonal relationships that permit each person their own biography, in harmony with others. It is the level of human psyche.

The enormous plasticity of the brain throughout life, and especially during infancy and adolescence, makes it so much so that the cerebral structure and the functionality of all people is configured in a very sensible manner to their experiences, life’s lessons, decisions, addictions and especially their interpersonal relationships, upbringing and culture. Thanks to brain plasticity¹, especially between puberty and the end of adolescence, there are no two brains alike as there are no two people alike be them females of males and be what their sexual orientation is.

This paper positions itself in this perspective and intends to offer the recent progress of the neurobiological sciences that help to have rationality; free of prejudices and conscious of the need for a clear and profound knowledge of the nature of homosexuality, a question that neuro-science has a lot to contribute².

Male brain and female brain construction

It is well established that a difference between the structure and the strategies -circuits by which information flows to process an event- proper of a female and a male brain exists. The cause of the differences is firstly the genetic endowment of the XX or XY. A gene situated on the Y chromosome initiates in males the masculinity program and to the hormones of the brain cells deters the feminine pattern. In women, the female pattern gets underway by the double doses of genetic information that the XX pair contributes and by the absence of the Y. During embryonic development, in doses and in different times, the sexual hormones appear of one or the other sex and the molecules of the cells that engages them, the receptors, so much so in the gonads as in the brain. Therefore, it is established, before birth, the brain design of each one with a masculine pattern of asymmetric hemispheres, or feminine with hemispheric symmetry³ and areas with diverse size in one or the other.

What is important of the design is not the relative sizes of one or other regions, but how the connections between them are established allowing for, or on the contrary hindering, the processing of information that flows through the fibers and fascicles of white matter between regions more or less away from the brain structure. Brain activity depends on these circuits that conduct neuronal information.

¹ Dulac, C. «Brain function and chromatin plasticity». *Nature* 465, 2010, 728-735. López- Moratalla, N. «Neurobiología de la adolescencia. El control del circuito afectivo-cognitivo». *Clínica y Análisis Grupal* 1, 2011, 31-48.

² López-Moratalla, N. «Fronteras del sexo biológico y cerebral en la transmisión de la vida». *Clínica y Análisis Grupal* 2, 2011, 35-60. López- Moratalla, N.» Una aproximación científica a la ideología de género: cerebro de mujer, cerebro de varón». En: *Persona y Genero*. Ed. Aranzadi. Thomson Reuters. Pamplona. 2011.

³ López Moratalla, N. *Cerebro de mujer y cerebro de varón*. RIALP, Madrid, 2007. 2ª edición.

The structure and functionality are created in a dynamic manner and principally in two windows of time in which there is a substantial influence of the sexual hormones: in the construction and maturation of the brain. In a first period, that spans the prenatal development and childhood, the exposure conditions the functionality between brain areas. Later on, from puberty on, the differences due to the hormonal doses and the localization of their receptors, unites to the fact that the hormonal production, lineal in males and cyclical in females. Sexual dimorphism is consolidated during the adolescence stage precisely when influences and especially the lessons and experiences of this moment in life are more intense, in which each one develops their identity sign, and the force of sexuality bursts in their life.

Today we have evidence that hormones play an important role from puberty on in the development and maturation of the brain⁴, and how it is done. Generally, testosterone and estradiol are associated with the dynamic changes in the brain in this period. The maturation of the parietal and temporal lobes and the prefrontal cortex is related with the rise of the levels of estradiol in girls and the increase of the levels of testosterone in boys. The wave of maturation that starts from the nape towards the forehead goes at different speeds in different areas of the two sexes, consolidating the prenatal brain pattern as masculine or feminine. The fluctuations in the relationship of the concentrations of the diverse hormones modify the layout of the trajectory that is being drawn up in those times.

The differences according to sex in the anatomy, the physiology and neurochemistry of the brain, are real and of clinical importance⁵. Differences exist between women and men with respect to neurological and psychiatric illnesses, which affect their nature and their incidence.

Some author has suggested⁶, and many others have thought, that considering the profound fascination of the public with the investigation about sexual difference, and its impact on mental health problems, the upbringing and labor equality, the neuroscientists should pay more attention that a misappropriation is not produced due to the so-called “scientific findings on the masculine and feminine brain”. Much too frequently the information, provisionally very validated, has been used to support ideological stands taken beforehand. Literature on the brain difference is full of extrapolated and badly interpreted statements.

⁴ Entre otros: Dinov, I.D., Worthman, C.M., Sowell, E.R. «Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity». *Cerebral Cortex* 21(3), 2011, 636–646. Giorgio, A., Watkins, K.E., Chadwick, M., James, S., Winmill, L., Douaud, G., De Stefano, N., Matthews, P.M., Smith, S.M., Johansen-Berg, H., James, A.C. «Longitudinal changes in grey and white matter during adolescence». *Neuroimage* 49, 2010, 94–103. De Bellis, M.D., Keshavan, M.S., Beers, S.R., Hall, J., Frustaci, K., Masalehdan, A., Noll, J., Boring, A.M. «Sex differences in brain maturation during childhood and adolescence». *Cerebral Cortex* 11, 2001, 552–557. Raznahan, A., Lee, Y., Stidd, R., Long, R., Greenstein, D., Clasen, L., Addington, A., Gogtay, N., Rapoport, J.L., Giedd, J.N. «Longitudinally mapping the influence of sex and androgen signaling on the dynamics of human cortical maturation in adolescence». *Proceeding National Academic Science USA* 107, 2010, 16988–16993.

⁵ Bao, A-M., Swaab, D.F. «Sex Differences in the brain, behavior and neuropsychiatric disorders». *The Neuroscientist* 16, 2010, 550–565. Klein, L.C., Corwin, E.J. «Seeing the unexpected: how sex differences in stress responses may provide a new perspective on the manifestation of psychiatric disorders». *Current Psychiatry Report* 4, 2002, 441–448. Cahill, L. «Why sex matters for neuroscience». *Nature Reviews Neuroscience* 7, 2006, 477–484. Shors, T.J. «Opposite effects of stressful experience on memory formation in males versus females». *Dialogues in Clinical Neuroscience* 4, 2002, 139–147.

⁶ Eliot, L. «The Trouble with Sex Differences». *Neuron* 72, 2011, 895–898.

Unquestionably, studies on sexual orientation are not easy studies. Until recently, with the same data, for some the sexual differences of the brain, because they are biological, are necessarily innate and fixed up to the point of constituting a personal condition. For others, gender is a socially “built” concept that has no assumptions either on the biological reality or on the psychological. One is born like that, the first ones claim: one is made in that way states the second group. The conclusions that are derived from an optional sexual orientation, and variable or not throughout life, or determined since birth, exert, obviously a strong influence in the way humans have of seeing each other, on culture, and interminable ideological debates have gone on in the last decades. Simultaneously, the response has consequences of great effects on social and family policies.

However, advances in neurobiology allow answering questions made long ago about homosexual orientation. The great amount of studies of different qualities has more concordances those disparities, from the moment that more can be known on the activity and circuits of the sexual brain.

As recently as August 1 of 2012, Rieger⁷ and collaborators published a new system to measure the excitation provoked by a sexual stimulus that contributes the necessary thoroughness to the answers given in the last years, since it allows confirming the concordant results of numerous studies that had been undertaken. Measuring the pupil dilation before erotic visual stimuli as an automatic parameter and unconscious of genital excitation -so difficult in measuring and making it comparative in males and females-, has permitted to be able to recount with so much difficulty the number of volunteers for the experiments that shed significant statistical results. With these measurements, many of the results obtained previously are validated.

Some factors that have complicated the study of human homosexuality

Behavior Bias

Sexual orientation does not have in humans the brain determinism of the genetic sex nor of gonad sex. However, the sexual differentiation of the rat also does not have reversibility. It has been described that in the adult female the stimulus of odor of the active pheromones of the brain centers of female sexual behavior and inhibit the masculine⁸. The lack of stimulus exerts the contrary effect can develop feminine behavior in males. Studies carried out with animals have assumed a behavior bias type for humans. Certainly, some aspects of sexual behavior in rodents have been useful to formulate biological basis on sexual determination, its hormonal control, including the cerebral circuits that underlie the responses of sexual stimulus⁹. The genetic and hormonal mechanisms can be analyzed in them very easily, since in rodents they are automatic processes where the relation “genetic cause” and

⁷ Rieger, G., Savin-Williams R.C. «The Eyes Have It: Sex and Sexual Orientation Differences in Pupil Dilation Patterns». *PLoS ONE* 7, 2012, e40256.

⁸ Kimchi, T., Xu, J., Dulac, C. «A functional circuit underlying male sexual behaviour in the female mouse brain». *Nature* 448, 2007, 1009-1014

⁹ Juntti, S.A., Coats, J.K., Shah, N.M. «A genetic approach to dissect sexually dimorphic behaviors». *Hormones and Behavior* 53, 2008, 627-637.

“effective response” is direct. These studies show a clear morphological sex difference between both sexes at an animal brain level. One of the first papers¹⁰ showed sexual dimorphism in the nervous centers of the sexual brain, upon finding that nuclei of the hypothalamus anterior presented a different volume in male rats than in female ones.

In humans, differences have also been described¹¹ in the size of these and other brain areas, although it always has not been able to be verified. Posterior meta-analysis have shown that the differences in symmetry or asymmetry can refer to very specific functions and that many of the measurements show differences more subtle than the generalizations made by the disclosure of the information. Above all, however, the human brain is plastic, liberated from the automatisms of the neurological processes of the animal brain. All that it experiments, lives, feels, decides leaves an imprint on the brain and those continuous changes go characterizing its own biography.

Until recently, we have not relied on longitudinally studies, especially during childhood and adolescence, in order to enable to analyze the differential dynamics of the maturation of brain areas¹² and their functional dimensions regarding neurotransmitters production or as far as its functional metabolic response or gene expression.

What is genetic or what is cultural in human sexual orientation cannot be extrapolated without further ado from the experiments on rodents. Only in human beings, when concerning the dimorphic cerebral configurations based on genetic and hormonal factors too, the influences received in social relationships, during upbringing and especially during the critical developmental stages, are very intense for the identity, the personality, and the sexual maturity of each person.

In that case, the clinical observation of patients with Kluver-Bucy syndrome, that presents itself with lesions in the temporal lobe and changes their orientation from heterosexual to homosexual, and the changes in sexual orientation in that same sense with people with tumors in the temporal lobe and in the hypothalamus. All this has allowed for it to be known that the neuronal functional correlative that underlies human sexual orientation, are the ones that process the response to sexual stimuli, differently in males and in females¹³. This fact has given access to the knowledge of the sexual brain of people, in the search for the origin of homosexuality without the need for dangerous extrapolations since the experiments with rodents.

The claim that homosexuality is present in the animal kingdom

¹⁰ Gorski, R.A., Gordon, J.H., Shryne, J.E., Southam, A.M., «Evidence for a morphological sex difference within the medial preoptic area of the rat brain». *Brain Research* 148, 1978, 333-346.

¹¹ Swaab, D.F., Hofman, M.A. «Sexual differentiation of the human hypothalamus in relation to gender and sexual orientation». *Trends in Neuroscience* 18, 1995, 264-270.

¹² Neufang, S., Specht, K., Hausmann, M., Gunturkun, O., Herpertz-Dahlmann, B., Fink, G.R., Konrad, K. «Sex differences and the impact of steroid hormones on the developing human brain». *Cerebral Cortex* 19, 2009, 464-473. Peper, J.S., Hulshoff Pol, H.E., Crone, E.A., van Honk, J. «Sex steroids and brain structure in pubertal boys and girls: a mini-review of neuroimaging studies». *Neuroscience* 191, 2011, 28-37.

¹³ Savic, I., Garcia-Falgueras, A., Swaab, D.F. «Sexual differentiation of the human brain in relation to gender identity and sexual orientation» *Progress in Brain Research* 186, 2010, 41-65.

There is evidence that homosexual orientation does not exist in the animal kingdom. Certainly, in non-human primates there exists an apprenticeship of the social “aspects” and the sexual behavior by imitation¹⁴. Theoretically, a practice of this type necessarily had to have suffered elimination, a negative selection by natural selection: it is incongruent that nature searches for methods of “birth control” when the decrease of fertility of a population puts in danger of extinction a species.

In reality some animals, the bonobos among others¹⁵ have sexual contacts between individuals of the same sex, this activity has not been eliminated by natural selection because it fulfills a function: it is an integration activity in social life, as in the same way as how in other species the mutual grooming is practiced. This is the political cement of its society among females, its expression of attention of the mothers towards their young, greetings, appeasements mechanisms before the frictions for the possession of food, or of territory. However, no animal limits its sexual activity with individuals of the same sex. All those that have activity with those of the same sex are promiscuous and bisexual.

Sexual behavior in animals is an innate automatism, and also learned, selected in function of reproduction, that cannot be translated to sexual orientation and the attraction between human beings, in which cognitive, emotional, affective components are integrated. All people have the capacity to loosen the bondages that tie the powerfully visceral sexual stimuli and respond to them or do not respond, personally.

The repetition of the idea that natural selection, which obviously awards fertility, could work in its contra, letting pass through its filter animal homosexuality, has propitiated the concept “effect of the fraternal birth order in human male homosexuality”. Several publications, not confirmed, proposed¹⁶ that for a boy to have several older brothers from the same mother increased, in approximately 33%, the probabilities of being homosexual, without taking into account at all the number of older sisters. This relation, when it exists, could be explained by the exposure rate to hormones in the prenatal stage. If in each of the successive pregnancies of males increase the mother's immunity against the determining factor of the male sex produced by the fetus, would diminish the masculinity of the posterior masculine fetuses¹⁷.

There is data in support that the order in birth lowers the exposure to androgens during prenatal life and it is in what order of the scale of male brothers influences in the parameter

¹⁴ Kahlenberg, S.M., Wrangham, «Sex differences in chimpanzees' use of sticks as play objects resemble those of children». *Current Biology* 20, 2010, R1067–R1068. Edelmann, N., Auger, A.P.«Epigenetic impact of simulated maternal grooming on estrogen receptor alpha within the developing amygdala» *Brain, Behavior and Immunity* 25, 2011, 1299-1304.

¹⁵ De Waal, F. «Tension Regulation and non- reproductive functions of sex among captive Bonobos». *National Geographic Research* 3, 1987, 318-335; De Waal, F. *El mono que llevamos dentro*. Editorial Tusquets, Barcelona, 2007.

¹⁶ Blanchard, R., Bogaert, A.F. «Homosexuality in men and number of older brothers» *American Journal Psychiatry* 153, 1996, 27–31. Blanchard, R.«Birth order and sibling sex ration in homosexual versus heterosexual males and females» *Annual Review Sex Researches* 8, 1997, 27–67. Jones, M.B., Blanchard, R. «Birth order and male homosexuality: extension of Slater's index» *Human Biology* 70, 1998,775–787.

¹⁷ Blanchard, R., Klassen, P. «HY antigen and homosexuality in men» *Journal Theory Biology* 185, 1997, 373–378.

that measures said prenatal exposure¹⁸. It deals with, as it will be commented; further ahead the asymmetry of the right hand. Today we know that the sensibility to prenatal exposure to testosterone predisposes to male homosexuality whose cause is based on multiple factors. The attack of the mother's immunological system to the factors initiates the masculinity program can be a possible influence in some cases.

Some have extrapolated this information and the suggestions of authors, interpreting that male homosexuality as a natural method of birth control. Before making such a fact scientific, it will be necessary to confirm that the position that he occupies between brothers causes homosexual orientation. Although this is so, men are not designated to reproduce to maintain the species; the transmission of life is a personal project. Controlling offspring is definitely a question for the heterosexual couple.

Current contributions of the neurosciences to sexual orientation

Current techniques of the neurosciences “measure” the emotions unleashed before a stimulus. This nuance is important because a part of detectable emotions intrinsically depends on the rational comprehension that the person has concerning their sexual orientation and a great amount of cultural factors, of upbringing, etc. Because of this, the design of an experiment is more important than the fact that the measurement be significant.

The areas of the sexual, social and emotional brain -hypothalamus, thalamus the brain amygdale and the hippocampus – mature in a different way for each sex, the same as other many areas¹⁹. In this case with the added particularity of being characterized since it has a high density in receptors of the sexual hormones. Consequently, its maturation from puberty on reaffirms or dilutes the prenatal pattern of feminine or masculine response to the sexual stimuli and is modified with the sexual experiences and lifestyles.

Before an erotic stimulus -visual, tactile, or olfactory- the areas of the sexual brain - different in males and in females- process the stimulus and the response that is an emotional motivation, a desire somatized as genital excitation.

The response pattern to the sexual stimulus is different in males and in females and employ different connections of the brain amygdale and specific areas of sex of the hypothalamus. Because of this the cerebral organization of sexual orientation also is.

Male Homosexuality

A data of enormous importance is that the maturation of the sexual brain, outlined in prenatal life with a feminine or masculine pattern, is affected by the genetic variant of

¹⁸ Blanchard, R., Cantor, J.M., Bogaert, A.F., Breedlove, S.M., Ellis, L. “Interaction of fraternal birth order and handedness in the development of male homosexuality” *Hormonal Behaviors* 49, 2006, 405-414.

¹⁹ Savic, I, *op. cit.*12.

androgen receptor that is inherited in the genome²⁰. This gene is situated on the X chromosome and has two variants, one of a high efficiency to unite the testosterone and the other of a low efficiency. Men, because of their XY endowment, only have one copy: what the X chromosome carries, necessarily being of maternal origin. According if the copy were the efficient or less efficient one it will have an innate predisposition respectively to heterosexual or homosexual orientation. The predisposition assumes differences in the connections of the sexual brain and to its physiology as far as the sensibility to testosterone. Thus, in the heterosexual male the attraction is provoked practically exclusively by women while in the homosexual male is almost exclusively by men. In this sense it is very rigid, so there actually does not exist in innate and spontaneous manner bisexuality.

The origin of a genetic predisposition in male homosexual orientation has as factors, apart from the less efficient copy of androgen receptor, mutation in DNA areas that regulate brain genes implicated in the metabolism of hormones. This factor makes that the innate predisposition be of different intensity.

Response, genital excitation, requires the activation of different areas than in the heterosexual male. It is not identical neither in intensity nor does it follow the same strategy the response to the stimulus of a man ante a woman or another man.

Therefore, what does male homosexuality mean?

The modification of sensibility to testosterone changes the organization of the areas of the sexual brain -brain amygdale/hippocampus- that process the sexual orientation. The erotic stimuli -for example, visual- as any other stimulus, reach the amygdale as “cold” where it is translated as an emotion. This emotion is then evaluated, with support from other areas, of attraction or rejection, of reward or punishment, always depending on the biological significance of the stimulus. The amygdale passes on the information, the desire, or the motivation, to the hippocampus that somatizes the emotion as genital excitation.

That the desire is aimed at the attraction of people of the same sex signifies that the sexual stimulus has been disconnected from its biological meaning: reproduction. That is to say that the genetic predisposition is translated in the brain in a disconnection of the desire of the objective that spontaneously and naturally that desire pursues. Said in another manner, human homosexuality presumes a dysfunction in cerebral organization, by which sexual pleasure is situated in areas outside the scope of the transmission of life.

As in all genetic predisposition and regulation of genes the physical means and the medium that we can call biographical and cultural, of life lessons and experiences, act on the DNA contributing to gene regulation; in particular in the apparition of hormonal receptors. It intensifies or dilutes the modifications more or less intense of the brain pattern. Thus,

²⁰ Perrin, J.S., Herve, P.Y., Leonard, G., Perron, M., Pike, G.B., Pitiot, A., Richer, L., Veillette, S., Pausova, Z., Paus, T. «Growth of white matter in the of white matter in the adolescent brain: role of testosterone and androgen receptor” . *Journal Neuroscience* 28, 2008 9519-9524..

although male sexual orientation is not spontaneously flexible, obeying an innate predisposition, this predisposition is consolidated, or to the contrary reduces the intensity with childhood and adolescent experiences. Male sexual orientation, according to the intensity of the innate modification of the brain pattern, is easier or more difficult to change in the other sense.

Therefore, if the person wishes, they have the right to be freely able to look for the psychological help that it needs. The option to look for help to orient their biography should not be stigmatized neither the person nor the psychiatric practitioner or psychologist that assists them.

Female Homosexuality

The female genetic make-up of XX allows having two androgen receptors of the efficient type, or two of the less efficient type or one of each type. Only in the first case, the greater sensibility to the androgens contributes a certain amount of masculinization of the feminine cerebral pattern. Therefore, female homosexuality is less frequent than the male, it is flexible, and changes in some stages of life and, in fact, homosexual females are spontaneously bisexual. There is not a genetic predisposition in females but a certain masculinization of the sexed brain that processes the sexual stimuli.

The difference between male and female homosexuality can help to revise many of the given explications. By the example of the one that contributes to the actual psychoanalysis²¹: “sexual attraction is a particular form of commitment of the I/other relationship that so much serves to consolidate the position of initial gender, as well as expanding the capacity of potential gender. Heterosexuality consolidates the masculinity of a male and the femininity of a female. The desire of a woman to “expand herself” in her masculinity and the desire of the male to explore his femininity, is assumed optional in heterosexual couples. This vision of sexual orientation as a fluid and changing reality has no support in the neurosciences. However, in accordance with the information collected and revised in this paper, we can say that in men the sexual attraction to people of the same sex, experimented and lived, consolidates the innate predisposition and can also eventually render in an acquired tendency; in the same manner the lifestyles can deconsolidate.

On the contrary, in women homosexuality/bisexuality corresponds more to the desire of spreading their masculinity. In the female population there appears of each person, a romantic attraction for people of the same sex²², which has been considered as homosexuality of expansion. On the other hand, it has been described that the sexual orientation of homosexual females, more than of male homosexuals reverts with more ease to be it spontaneously or with psychotherapy²³.

²¹ McKenzie, S. «Genders and sexualities in individuation: theoretical and clinical explorations» *Journal of Analytical Psychology* 55, 2010, 91-111.

²² Jorm, A.F., Dear, K.B. et al. “Cohort difference in sexual orientation: Results from a large age-stratified population sample”. *Gerontology* 49, 2003, 392-395.

²³ Spitzer, R.L. «Can some gay men and lesbians change their sexual orientation? 200 participants reporting a change from homosexual to heterosexual orientation». *Archives of Sexual Behavior* 32, 2003, 403-492.

In conclusion, homosexuality appears in neurobiological investigation as a process neither irreversible nor merely optional, as if it were dealing with a continuous slider in one orientation or another according to pressure on the environment of a personal decision. It has as its base a genetic predisposition, influenced by the physical-physiological surroundings, and receives the positive or negative influences in family and social relationships, with the upbringing, particularly during critical stages of development. These influences are very clear-cut for identity, personality, and sexual maturity of each person. They are not indifferent.

The cerebral reality that neurosciences show us could be the meeting point for a debate that thoroughly analyzes the model for a heterosexual relationship, implicated in the transmission of life in which the future of society depends on, and the model of a homosexual relationship.

It is necessary to know and inform to society the effects-indifferent or adverse - in the psychological and emotional development of the following generations, if we admit without further ado the option that the family where they are raised is artificially constituted by two fathers or two mothers, or naturally by one father and one mother.

Many are the brain functions of all the people that require *alignment* with the masculine brain of the father, or whoever acts as such, and with the feminine brain of the mother or maternal figure, at least during the first two years of life²⁴, to reach a harmonious development and mental health. In the family based on the natural heterosexual model, the absence of whichever of the parents is replaced and replaceable. The model of cohabitation that arises from a homosexual relationship does not try to replace a lack but to present as a reality that has as a duplicate one of the figures and inexistent the other.

The information –with a strong intention of avoiding and type of bias- of neuro-scientific progress with reference to homosexuality could facilitate a rational debate, when it is still in its beginnings. It is possible that with time the outcome of an experiment of this type calls for the return to an education and upbringing in a natural coexistence. By then, it will be late to remedy the possible harm caused, to those that were not even given the opportunity to choose.

DYNAMIC BRAIN AND SEXUAL ORIENTATION HOMOSEXUALS, ARE THEY BORN? ARE THEY MADE? A MISCONCEIVED MATTER

Abstract

This review provides recent advances in neurobiological science on brain dynamics, which have established structural and functional differences between the brains of men and women with homosexual heterosexual orientation. Data show that there is no genetic determination. In men's homosexuality exists an innate predisposition exists, mainly

²⁴ Gao, W., Gilmore, J.H., Giovanello, K.S., Smith, J.K., Shen, D., et al. «Temporal and spatial evolution of brain network topology during the first two years of life». *PLoS ONE* 6(9), 2011, e25278.

associated with genetic variants in the androgen receptor located on chromosome X. The effectiveness of the receptor modulates the masculinity pattern of brain maturation in both sexes during the prenatal period and adolescence, precisely coinciding with maximal brain plasticity. The inherited predisposition in men would be associated with epigenetic mutations in the system that regulates gene expression in the brain depending on the medium. The brain pattern, different in men and women, is directly related to early exposure to steroids of sexual brain areas as well as many other regions. The architectural structure and functional brain is consolidated or becomes diluted by the cultural/biographical experiences in relation to the environment. Memories, emotions, early sexual experiences, etc. play a part as well-so that the innate predisposition trend can establish itself as acquired by the social, educational factors and family, or can be diluted with more or less difficulty, depending on the strength of predisposition. The sexual brain consists of nuclei of the hypothalamus and amygdaloidal complex of the limbic system and controlled by the frontal lobe. The homosexual brain pattern, when the inherited predisposition becomes acquired tendency, shows in the functional and structural dimorphic traits, not directly related to sexuality, values that are closer to the pattern of people of the other biological sex. However, the pattern of response to sexual stimuli is different in male and heterosexual men. In homosexual women, the response pattern is masculinized. Homosexuality appears in neurobiological research as a process neither irreversible, nor purely optional, there is a system dysfunction in the assessment of sexual stimuli in relation to their biological function, reproduction. The data should be taken into account in order to respect the right of those who wish to try to change their sexual orientation. In addition, for making social and legal decisions that equate both types of relationships, which have implications for current social life and next generations.

Key words: gender differences, sexual orientation, genetic predisposition, sexual brain, brain structure.

1. Genetic determinism of sex does not include determinism of human homosexual orientation

1. Genes-medium-culture

The idea of a rigid and mechanistic genetic determination, in the characteristics and individual aptitudes of each one, is now obsolete. It is obvious that a gene does not exist – nor various genes- of homosexuality, as a violence gene does not exist, or of intelligence. The mutation of a gene can certainly give rise to congenital or inherited “monogenetic” diseases many of which we know. In them, if the damaged gen (or genes) has a function in a certain organ, liver, brain, etc., that will generate a liver disease, brain, etc.

The human genome is made up of 23 pairs of chromosomes. Each pair is formed by the chromosome inherited from the mother and the one inherited from the father. Apart from the maternal copy and the paternal from each gene, there exists, for some genes, variable copies from the same in the chromosomes of pair. These forms of a gene give way to the same protein, but each one possesses different characteristics and a major or minor activity. The type of copies that are received in the inheritance is in the base of some type of *genetic predisposition*.

In sexual orientation a base that is assumed is, as will be dealt with later on, the two types of receptors of androgens. For being in the chromosome X, the male can only have the efficient or inefficient copy. On the contrary, in the female, the two XX contribute a variety of possibilities: very inefficient, media and very strong effectiveness in the capture of the hormone and, for that matter, of the sensibility to its effects.

This mode of *inherited predisposition* to some human characteristic, based on several copies of a gene, is not the only one.

The branch of Biology, that is called Epigenetics, allows us to know how in the development of an individual, of each of his organs and, thus, of the functions of each one, is dependent on the medium. The concept of *environment* refers to the factors that are going to act on the genes – on the *genome* of each one- permitting that an own protein of that organ, at that age, etc., or remains silent forever, or during some time, is a concrete part of the organism. This system of regulation changes in structure gradually and orderly with its surroundings, also continuously changing.

The internal regulatory factors appear throughout embryonic development and throughout life in the diverse parts of the organism. The external factors of the organism are the embryo's environment –the mother, during embryonic development-, and the environment in the broad sense of the word, of the surroundings, diet, etc., after birth.

The relationship genes/environment is called *epigenetics*. It assumes that DNA, without changing the sequence of its ashlar, orderly changes its DNA spatial structure or the methylation pattern: the site and number of the chemical markings of one of its DNA bases, the cytosine, that incorporates or eliminates a methyl group.

As genetic mutations occur –that change the sequence of the four bases that form the DNA thread and therefore affect the genome-, there exists *genetic mutations* or *epimutations* that modify the called epigenome. These epimutations are transmitted to the offspring, in the same way as the genetic mutations. How the genetic mutations affect the function of the protein encoded by a gene, epigenetic mutations the control of the expression of one or several genes.

In the topic that concerns us among those factors of gene regulation sexual hormones have a special importance. Manufactured in the gonads and in the brain –and partially in the adrenal glands- they mark the rhythm of female gonad construction –the ovaries- or male –the testicles- following the guidelines of the genes present in the female sexual chromosomal pair, XX, or the male, XY.

Brian cells, the neurons, as any other cell of the organism possesses a pair of XX or XY chromosomes according to the sex and that contain the different sexual characteristics in the feminine body or in the masculine, a sexed organ.

It, also, is the most complex organ in any mammal and in a special way in humans. It realize a multitude of functions with a certain independence, with a cabling that unites the

circuits of some areas with others, with two hemispheres, four lobes in each hemisphere and three layers connected amongst them, that process the visceral, the emotional and the cognitive. We find ourselves, thus, with a level of complexity of gene association/medium greater than in any other and that by being regulated by the sexual hormones, differs in men and women in structural and functional brain organization. For example, the concentration of a hormone –medium- modifies the pattern of regulation of the gene that codifies its receptor. The receptors are proteins of the membrane or of the interior of the cells that unite the hormone and transmit the signal of its presence in genes, thus exercising a regulatory effect on them.

Together with that complexity of development and maturing of the sexed brain organ, in human beings we find a second level of complexity: the brain of each one is plastic. This is, throughout life, especially in adolescence, the construction of the brain of each one of the persons; it is carried out with one's own life: relationships, life's lessons, experiences, memories, decisions, etc. All of them leave a mark: they epigenetically modify the brain. This is, causes changes in the gene expression of neurons and with it reinforces, weakens or creates new brain circuits that process the knowledge, emotions, etc. Life works what has been received, the innate and each one does it in one sense or another for the different human abilities, with their own decisions and the ineludible influence from others. It is the cultural level of life, the psyche of each one, intrinsically melted with biological life.

This means, therefore, that to study a brain property like sexual orientation, demands to study the genes, the regulation of its expression with development and life and the changes that one's own life continuously leaves in the mechanism of the regulation of the neurons of the implicated circuits.

It is the inseparable and distinct trio of *genes/medium/culture-biography*.

1.2 Gene effect

The biological determination of sex is determined on the first level by the sexual chromosomal pair. In the masculine fetus the masculinity pattern begins with the appearance of the determining sex factor from the gene (SRY) located on the Y chromosome²⁵. The development of the female sexual organs during the gestation is based mainly on the absence of the androgens, caused by the presence on the X chromosome of a gene repression factor –FOXL2²⁶- that impedes the development in the masculine direction and the lack of genes on the Y chromosome.

Together with the genetic endowment, the epigenetic information that appears with development and throughout life has a key role in the sexual differentiation of the brain.

²⁵ Dubin, R.A., Ostrer, H. «Sry is a transcriptional activator». *Molecular Endocrinology* 12, 1994, 1182–1192. Sekido, R., Lovell-Badge, R. «Sex determination involves synergistic action of SRY and SF1 on a specific Sox9 enhancer» *Nature* 453, 2008, 930-934.

²⁶ Williams, T. W., Carroll, S. B. «Genetic and molecular insights into the development and evolution of sexual dimorphism». *Nature Review Genetic* 10, 2009, 97–804. Uhlenhaut, N. H. et al. «Somatic sex reprogramming of adult ovaries to testes by FOXL2 ablation». *Cell* 139, 2009, 1130–1142.

The surroundings of a developing neuron, be it because of its genetic endowment XX or XY, is formed by the nervous cells that surround it and the hormones that it produces, as well as the hormones, nutrients, medications and other chemical substances of the mother that enter in fetal circulation through the placenta. It takes place in different moments other than the formation and maturity of the gonads.

Sexual identity is guided and is determined in the brain by fetal hormonal exposure. This is done in an independent form from the structure and the mechanism of the gonads. Hence, for example, there being the existence of the human phenomenon of transsexuality, the feeling of having a body with a mistaken identity. It is known that it is due to a congenital genetic defect, that in male-to-female transsexuals, it deals with the genes of the metabolism of androgens, the aromatase, and the receptor genes of these hormones.

Can it be stated that homosexuality is a prenatal determination in what is referred to as gene alteration? The answer is negative to a determination of this type. Studies deny the existence of causal genetic bases responsible for homosexuality.

However, many other data show the existence of an *inherited predisposition*, at least in male homosexuals.

1.3 Two forms of the androgen receptor gene: possible genetic predisposition to homosexual orientation

A genetic predisposition to such a complex function as is sexual orientation has to consist in a factor that plays a key role in specific neuronal circuits of the sexual brain. This involves the hypothalamus, the brain area that processes the vegetative aspects of sexual stimulation and the brain amygdala that processes/evaluates the response to the stimulus and contacts with the frontal lobe, which controls the response.

A priori, a good or the best candidate to generate a predisposition of this type would be the receptor androgen gene.

In human beings the exposure to testosterone seems to be the main mechanism implicated in the differential structure of the brain, not only due to the different concentration of the hormone, according to sex, but to the temporal-spatial expression of the androgen receptor in different areas, very different in the areas of the masculine or feminine sexual brain.

The biggest evidence that the activity of the receptor of androgens is a key element in human masculinization is the fact that the mutation in the receptor gene that generates complete androgen insensitivity syndrome make, in spite of having/possessing a masculine genetic (XY), the individuals affected develop phenotypically as females. This physical feminization is so marked that generally the diagnosis is not made until puberty before the lack of menstruation²⁷, has the identity of female gender –except for some exceptional

²⁷ Hines, M. «Early androgen influences on human neural and behavioral development». *Early Human Development* 84, 2008, 805-807.

case²⁸ - and are heterosexual women²⁹.

Additionally, the “short” gene is highly functional, with great affinity by the testosterone and has been associated to an accentuation of various phenotypes of somatic differentiation in males³⁰ and in women with hyperandrogenism syndromes³¹.

The relative inaccessibility to the human brain has hindered the knowledge of the dynamics of differential feminine and masculine brain development. With the studies of Raznahan’s team³², we provide a detailed longitudinal map of differential brain development, of the two brain hemispheres during the adolescent period, from the age of nine to twenty two years of age. Apart from the different maturing process in diverse areas, this study shows the effect that on “masculinization” of the cortex areas have the forms of the receptor, of a different efficiency, in men as well as in women.

The study has classified the participants in groups according to the type of receptor: the efficient short and the other “long”, less functional. Obviously, by this gene being linked to the X chromosome, males only possess one of the two types, while women possess two and can have an intermediate, high, or low effectiveness. Therefore, it has been possible to associate the genotype of the androgen receptor with the velocity of the maturing of diverse cortical areas of both hemispheres in males and females. In effect, it has been observed an “effective dose” in the masculinization of the brain cortex linked to three situations of different effectiveness of the androgen receptors.

Data shows strong evidence that the union of the androgens modulates the development processes of the human brain in specific areas, in a specific form for sex. The greatest effectiveness of the receptor in males is associated to a greater masculinization of the pattern of bilateral cortical maturity of the parietal inferior lobe. This region processes the visuospatial tasks where males statistically have a greater ease. However, the greater effectiveness of the androgen receptors of females is specifically associated with the more masculine pattern of the maturing of the inferior frontal gyrus in the left hemisphere, implicated in language and in control of the impulses, much easier tasks for women and that precisely, becomes more difficult in the menstrual cycle phase of high estrogen level.

28 . T’Sjoen, G. et al. «Male gender identity in complete androgen insensitivity syndrome». *Archives of Sexual Behavior* 40 (3), 2011, 635-638.

29 Wisniewski, A.B., Migeon, C.J., Meyer-Bahlburg, H.F., et al. «Complete androgen insensitivity syndrome: Long term medical, surgical, and psychosexual outcome». *Journal of Clinical Endocrinology and Metabolism* 85, 2000, 2664–2669

30 Zitzmann, M. «The role of the CAG repeats in the androgen receptor polymorphism in androl- ogy». *Frontiers of Homone Research* 37, 2009, 52-61.

31 Van Nieuwerburg, F., et al. «Shorter CAG repeats in the androgen receptor gene may enhance hiperandrogenicity in polycystic ovary syndrome». *Ginecological Endocrinology* 24, 2008, 669-673.

32 Raznahan, A., Shaw, P., Lalonde, F., Stockman, M., Wallace, G.L., Greenstein, D., Clasen, L., Gogtay, N., Giedd, J.N. «How does your cortex grow?» *Journal of Neuroscience* 31, 2011, 7174–7177. Raznahan, A, Lerch, J., Plee, N., Greenstein, D., Wallace, G.L., Stockman, M., Clasen, L., Shaw, P.W., Giedd, J.N. «Patterns of coordinated anatomical change in human Cortical development: A longitudinal neuroimaging study of maturational coupling». *Neuron* 72, 2011, 873–884

In summary, males and females with the genetic effective variant of the estrogen receptor shows a more masculine pattern of cortex maturity than others of the same sex that possess the less effective receptor. The difference in the levels of androgens, during the prenatal period and adolescence, between males and females³³ contribute to the differences of the cortical anatomy dependent on sex.

If this occurs in diverse brain regions, in the areas that form the sexual brain, very rich in hormonal receptors, the level of effectiveness of the receptors would mark the predisposition to sexual orientation. In males, the genotype with respect to the variants of the receptor of androgens supposes an innate predisposition heterosexual or homosexual sexual orientation. In women, it is less rigid because it always has two copies and the presence of the two of the very efficient type involves a certain masculinization of the brain patterns.

A genetic predisposition is not an illness of a genetic type: there is no gene mutation. It contributes a greater or a lesser sensibility to the action of a hormone signal. The expression of this gene, so much so in its effective form as in its being ineffective, suffers as all genes do an epigenetic regulation that permits it to express quantitatively in a greater or a lesser degree, according to the environment. An environment that is physical in the prenatal stage, physical and human after birth, and especially intense in both mediums in puberty and adolescence. Human surroundings -family relationships, upbringing, etc., - which make the predispositions, be either reaffirmed or diluted, influencing in a personal manner in the options and decisions of each individual.

1.4. Epigenetic effect in the predisposition to male homosexuality

Evidence is accumulated and shows that a strong component exists in the inheritance that influences in sexual orientation³⁴.

a) For many years, the cause of male homosexuality on the X chromosome³⁵, that necessarily is of maternal origin, Xm. Hamer's group centered its attention on the Xq28 region, situated in the endpoint of the long arm of the Xm chromosome³⁶, and similar

³³ Garcés, C., et al. «Hormone levels in 12-to 15 year-old boys and girls in Spain and their relationship with anthropometric variables». *Clinical Biochemistry* 41, 2008, 621-624. Garagorri, J.M. et al. «Reference levels for 17-hydroxyprogesterone, 11-desoxycortisol, cortisol, testosterone, dehydroepiandrosterone sulfate and androstenedione in infants from birth to six months of age». *European Journal of Pediatrics* 167, 2008, 647-653.

³⁴ Ngun, T.C., Ghahramani, N., Sánchez, F.J., Bocklandt, S., Vilain, E. «The genetics of sex differences in brain and behavior». *Frontiers in Neuroendocrinology* 32 (2), 2010, 227-246.

³⁵ Bailey, J.M., Pillard, R.C., Dawood, K., Miller, M.B., Farrer, L.A., Trivedi, S., Murphy, R.L. «A family history study of male sexual orientation using three independent samples». *Behavior Genetics* 29, 1999, 79-86. Kruglyak, L. Hamer, D. «Genetics and male sexual orientation». *Science* 285, 1999, 803. Sandovici, I., Naumova, A.K., Leppert, M., Linares, Y., Sapienza, C. «A longitudinal study of X-inactivation ratio in human females». *Human Genetics* 115, 2004, 387-392.

³⁶ Hamer, D., Hu, S., Magnuson, V., Hu, N., Pattatucci, A.M. «A linkage between DNA markers on the X chromosome and male sexual orientation». *Science* 261, 1993, 321-327.

patterns were found in homosexual people of some families. Later on it was confirmed, highlighting that, on the contrary, female sexuality had no relationship at all with this area³⁷.

A meta-analysis showed that homosexual brothers shared 64% of the structure of the Xq28 region, instead of the awaited percentage, 50%. This fact does not mean a lack of a possible determination, as has been posed³⁸. What backs up is a participation of the X_m chromosome, from the maternal line, of the regulation of the molecular mechanisms of sexual orientation. Indeed, the dynamics of activation/deactivation of the X chromosome³⁹ in women with or without homosexual sons or in women with two or several homosexual sons was analyzed. A slant was observed in the state of the area of that chromosome: mothers with one homosexual son have in respect with those that do not have any a 13% and those that have more than one have that area inactivated with a 23%.

Logically each male child receives from the mother only one X chromosome, that could be the one she received from her father X_p or that she received from her mother, X_m, and that are not alike amongst themselves. The alteration, of this zone Xq28 or any other, is in the mother's X_m, it explains, as has been described, in some families there is a higher rate of homosexuality amongst brothers and in the maternal aunt and uncle of homosexual men⁴⁰. Male sons receive the X_p; the X of the mother of paternal origin does not have this component of predisposition, which corresponds with the lack of relationship with paternal inheritance⁴¹.

b) Various studies would suggest an influence in the familiar inheritance in male homosexuality⁴², an inheritance that is not limited to one sole factor but to multiple ones. On the one hand, the match rates of homosexuality in monozygotic⁴³ and heterozygotic

37 Hu, S., Pattatucci, A., Patterson, C., Li, L., Fulker, D., Cherny, S., Kruglyak, L., Hamer, D.H. «Linkage between sexual orientation and chromosome Xq28 in males but not females». *Nature Genetics* 11, 1995, 248–256.

38 Rice, G., Anderson, C., Risch, N., Ebers, G. «Male Homosexuality: Absence of Linkage to Microsatellite Markers at Xq28» *Science* 284, 1999, 665–667.

39 Bocklandt, S., Horvath, S., Vilain, E., Hamer, D.H. «Extreme skewing of X chromosome inactivation in mothers of homosexual men». *Human Genetics* 118, 2006, 691–694.

40 Revisión: Bailey, J.M., Pillard, R.C. «Genetics of human sexual orientation». *Annual Review Sex Researches* 60, 1995, 126–150.

41 McKnight, J., Malcolm, J. «Is male homosexuality maternally linked? *Psychology Evolution Gender* 2, 2002, 229–239. Bailey, J.M., Pillard, R.C., Dawood, K., Miller, M.B., Farrer, L.A., Trivedi, S., Murphy, R.L. «A family history study of male sexual orientation using three independent samples». *Behaviour Genetics* 29, 1999, 79–86.

42 Kirk, K.M. Bailey, J.M. Dunne, M.P. Martin, N.G. «Measurement models for sexual orientation in a community twin sample, *Behavior Genetic* 30, 2000, 345–356. Kendler, K.S., Thornton, L.M., Gilman, S.E., Kessler, R.C. «Sexual orientation in a US national sample of twin and non-twin sibling pairs». *American Journal of Psychiatry* 157, 2000, 1843–1846. Bailey, J.M., Dunne, M.P., Martin, N.G. «Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample» *Journal Perspectives Social Psychology* 78, 2000, 524–536.

43 Bailey, J.M., Pillard, R.C. «A genetic study of male sexual orientation» *Archives Genetic Psychiatry* 48 (12), 1991, 1089–1096.

twins and on the other hand, in some cases but not in others, a homosexual person had an excess of homosexual members in the mother's family. If it dealt with one or various epimutations⁴⁴, it can be understood that its association would allow for potentiating, or on the contrary dilution of the innate predisposition. The relationship between genes and the prenatal medium, and the physical environment and cultural-biographical of postnatal life explains the existence of degrees and the greater or lesser ease to modify sexual orientation.

In this sense, it is of great importance the studies of Mustanski's team, in finding possible mutations of an epigenetic type, that is to say that they generate changes in the regulation of the genes according to their environment, in an attempt of finding a *multiple regulation* pattern of sexual orientation⁴⁵. For the first time, this team carried out a complete probing of the genome – 403 regions of diverse chromosomes- of homosexual men. There were 456 of 146 families with two or more brothers with homosexual orientation. The highest DNA coincidence happened in three regions, located on chromosomes 7, 8 and 10. They are epigenetic markings that, as correspond, modify the regulation of other genes. They could be of paternal or maternal origin and only one of the epimutations was exclusively of maternal origin and was localized on chromosome 26. Only in some families did the already famous Xq28 region appear.

This is to say that inherited epimutations exist in diverse regions of the genome. This could modify the expression of the genes on the sexual brain in a quantitative variable manner. An innate predisposition in the level of epimutations would be at the base of the differences of degrees of the innate predisposition.

What genes are there in those regulatory regions whose expressions could be affected? According to the splendid approach of this paper in the region (7q36) there is a gene that codifies an essential protein for the development of a brain area (suprachiasmatic nuclei located in the hypothalamus) implicated in sexuality⁴⁶. Both paternal and maternal inheritance contributes in the same amount and an increase has been described in that brain area in homosexual men⁴⁷. It also includes other genes that participate in the separation of the brain hemispheres during fetal development and in the right and left asymmetry. Precisely male and female homosexuals show a significant increase of the right asymmetry

⁴⁴ Bocklandt, S., Hamer, D.H. «Beyond hormones: a novel hypothesis for the biological basis of male sexual orientation». *Journal of Endocrinological Investigation* 26 (3), 2003, 8–12.

⁴⁵ Mustanski, B.S., Dupree, M.G., Nievergelt, C.M., Bocklandt, S., Schork, N.J., Hamer, D.H. «A genome wide scan of male sexual orientation». *Human Genetics* 116, 2005, 272–278.

⁴⁶ Morrison, C.F., Dorin, J.R., Piggins, H.D., Reubi, J.C., Kelly, J.S., Maywood, E.S., Hastings, M.H. «The VPAC (2) receptor is essential for circadian function in the mouse suprachiasmatic nuclei» *Cell* 109, 2002, 497–508.

⁴⁷ Swaab, D.F., Hofman, M.A. «An enlarged suprachiasmatic nucleus in homosexual men». *Brain Researches* 24, 1990, 141–148.

⁴⁸ Lalumiere, M.L., Blanchard, R., Zucker, K.J. «Sexual orientation and handedness in men and women: a meta-analysis». *Psychology Bulletin* 126, 2000, 575–592. Rahman, Q., Wilson, G.D. «Sexual orientation and the 2nd to 4th finger length ratio: evidence for organising effects of sex hormones or developmental instability?» *Psychoneuroendocrinology* 28, 2003, 288–303.

of the hand that is related with the asymmetry of the brain⁴⁸. The region near the 8p12 of chromosome 8 contains several genes that codify enzymes of the metabolism of various hormones implicated in sexual development⁴⁹.

Lastly, the 10q26 region of the maternal chromosome 10 contains *imprinted genes*. These genes, of which the human genome possesses some hundreds, keep the regulation pattern that corresponds to the chromosome inherited from the mother and from the chromosome inherited from the father. They are genes that do not erase these markings, nor are they reprogrammed or fertilized throughout its life. It means that only one copy can only necessarily be used or the other copy in each case in a fixed way. Therefore, if the only usable copy is mutated determines a known illness known as “linked with imprinting” that the majority of them have then with neurological disorders.

Why is this? Simply because a good part of imprinted genes exerts an essential role in the first stages of embryonic development, where the nervous system is being formed and developed. For some genes, the maternal copy is expressed and the paternal remain always silent. The mutation of the former will give way to an illness of maternal origin. For other genes that the copy that is silenced is the maternal, the alteration in the paternal will give origin to an illness of paternal origin.

What can a modification, epimutation in the maternal chromosome 10 region that has imprinted genes mean? The epimutation supposes that genes with imprinting will be expressed in greater or lesser amounts according to how the epigenetic mutation is.

The gene is normal; it cannot be considered that it gives way to an illness of genetic origin or simply to a potentiation or dilution of the innate predisposition. Moreover, this information is of great importance in that it offers support to the widespread idea⁵⁰ that the influence of the maternal inheritance in male homosexuality not only implicates the X chromosome but the other 22 non-sexual pairs of chromosomes, the so-called autosomal.

Summing up everything, we all receive genetic inheritance of our parents in two layers. One layer is the genome or the sequence of the base of the DNA polymer that does not change throughout its entire life and is the same in all of the organism's cells. It contributes the biological identity, naturally sexed, of each one. Then there is a second layer. This is the epigenetic layer, which does not modify the DNA sequence but its structure and chemical markings, and thus regulate gene expression. This is that it is expressed or not, that it does so with more or less intensity, in a specific moment and in a specific part of the organism.

The diverse inherited genetics in the first layer and the inherited mutations of the second

⁴⁹ Mustanski, B.S., Chivers, M.L., Bailey, J.M. «A critical review of recent biological research on human sexual orientation». *Annual Review of Sex Research* 12, 2002, 89–140.

⁵⁰ Incluso se ha publicado, aunque no confirmado, en la línea de una determinación genética, que una característica de madres de varones homosexuales es una mayor fecundidad (Iemmola, F., Ciani, A.C. «New evidence of genetic factors influencing sexual orientation in men: Female fecundity increase in the maternal line». *Archives of Sexual Behavior* 38, 2009, 393–399).

layer constitute the actors of the innate predisposition.

Lastly, in social perception it seems to be evident an increase in the number of people who make known their homosexuality. Is it a real increase or simply that it is not concealed as it was a few years ago? The answer would require continuing with studies on the environmental endocrine disruptors; diverse official reports bring to light the impact of these contaminants in the decline of human fertility. Recent data also show that such compounds can interfere during the early development with the sexual differentiation of the human brain. Plastic softeners, that is to say, phthalate esters, are omnipresent environmental chemicals with anti-androgen effects. The exposure to these compounds is accompanied with the reduction of the masculine pattern of play in male⁵¹, as also the biphenyls polychlorinated.

2. Hormone effects and their receptors in the brain

The effect of hormones on the brain is multifactorial and dependent of the stage of life. The diverse factors are the relationship pre and postnatal of testosterone and estrogen, the androgen and estrogen receptors and the degradation of the testosterone by the aromatase enzyme.

Steroids during the postnatal period contribute to the organization of the brain and influence the sexual preferences⁵² while the exposure to sexual hormones in adult life stimulates sexual behavior, but does not modify the orientation⁵³. The sexual brain matures in adolescence.

2.1. Prenatal stage

The hypothesis of the influence of hormones in the prenatal stage, so much so if it is due to genetic factors of the child as if it is because of the mother's situation, continues being the most accepted. The production of estrogens by the fetal testicle diminishes, for example, with maternal stress during the first months of pregnancy. In this first prenatal stage and during infancy the influence of the hormones on the brain is very pronounced⁵⁴.

The production of testosterone by the fetal testicles is high and its peripheral conversion in dihydrotestosterone is essential for genital formation. It reaches the brain in two surges. A first one occurs during the middle of the pregnancy; then the levels of testosterone are ten

⁵¹ Swan, S.H., Liu, F., Hines, M., Kruse, R.L., Wang, C., Redmon, J.B., *et al.* «Prenatal phthalate exposure and reduced masculine play in boys». *International Journal of Andrology* 33, 2010, 259–269.

⁵² Meyer-Bahlburg, H.F.L., Ehrhardt, A.A., Rosen, L.R., *et al.* «Prenatal estrogens and the development of homosexual orientation». *Developmental Psychology* 31, 1995, 12–21.

⁵³ Schwarz, J. M., Nugent, B. M., McCarthy, M. M. «Developmental and hormone-induced epigenetic changes to estrogen and progesterone receptor genes in brain are dynamic across the life span». *Endocrinology* 151, 2010, 1–11.

⁵⁴ Schwarz, J.M., McCarthy, M.M. «Steroid- induced sexual differentiation of the developing brain: multiple pathways, one goal». *Journal of Neurochemistry* 105, 2008, 561-1572.

times higher in boys than in girls. The second wave is produced in the first three months after birth.

Estrogens not only reach the brain by circulation but also by the action of the aromatase enzyme on the testosterone. The levels produced in the masculine fetus exert a defeminizing action. The female fetal brain is protected against the effect of the mother's circulating in the mother by the α -fetoprotein protein that is produced by the fetus and links with force to the estrogens⁵⁵. At the end of the pregnancy, when the levels of α -fetoprotein, the fetus is more exposed to the estrogens of the placenta so it loses the inhibition of the axis that from the pituitary sends signals to the gonads. Thus, at birth there is a peak of testosterone in males and a peak of estrogens in girls.

Therefore, the defeminizing action of estradiol is produced in males before birth and is avoided in female fetuses due to the protective action of the α -fetoprotein, while the feminizing action of estradiol normally occurs between birth and puberty when the ovaries produce high levels of estrogen and the α -fetoprotein does not act anymore.

During the intrauterine period, the interaction between the hormones and the genes in the development of the brain cells is decisive in the programming of the sexual brain, harmonized with genetic, gonad and genital sex. Hormones, in fact, do not only activate the functioning of certain brain areas but that organize the neuronal circuits. During fetal development, an immature outline is introduced in the design of the adult. Among other characteristics functional asymmetry from greater to lesser is established of the two hemispheres⁵⁶.

2.2 Asymmetry in the hands: A measure of prenatal exposure to hormonal steroids

Sexual differentiation leads to the development of different anatomical structures -gonads and genitals- and that also produces anatomical changes although less evident, in the brain, bones, muscles etc. Diverse bilateral anatomical structures are not perfectly symmetrical; some traits have directional asymmetry -differ in the right side or the left in an elevated number of individuals in a population - and they can constitute sexually dimorphic traits.

The relative length of fingers two or four of the hand poses a marker of sexual dimorphism linked to a greater exposure to steroids in the prenatal stage: the relationship of length between the second and the fourth finger (2D:4D) of the hands⁵⁷ in men and women is

⁵⁵ Bakker, J., De Mees, C., Douhard, Q., et al. « α -fetoprotein protects the developing female mouse brain from masculinization and defeminization by estrogens». *Nature Neuroscience* 9, 2006, 220–226.

⁵⁶ De Lacoste, M.C., Horvath, D.S., Woodward, D.J. «Possible sex differences in the developing human fetal brain». *Journal of Clinical and Experimental Neuropsychology* 13, 1991, 831–846. Chi, J.G., Dooling, E.C., Gilles, F.H. «Left-right asymmetries of the temporal speech areas of the human fetus». *Archives of Neurology* 34, 1977, 346–348. Gilmore, J.H., et al. «Regional gray matter growth, sexual dimorphism, and cerebral asymmetry in the neonatal brain». *Journal of Neuroscience* 27, 2007, 1255–1260. Diamond, M.C. «Hormonal effects on the development or cerebral lateralization». *Psychoneuroendocrinology* 16, 1991, 121–129

⁵⁷ Manning, J.T. «Resolving the role of prenatal sex steroids in the development of digit ratio». *Proceedings of the National Academy of Sciences of the United States of America* 108, 2011, 16143–16144.

different.

The differences, statistically significant, are due to the proliferation of the bone cells, the chondrocytes, of the phalanges of the fourth finger that increases by the prenatal testosterone and diminishes with the estrogens. Androgen and estrogen receptors are more abundant in the fourth than in the second finger. In such a way that the value of the relationship 2D:4D depends on the changes of the relationship androgens/estrogens on the fourth finger, during the window of fetal growth where the hands are developed⁵⁸. The correlation of the relative longitude with the relationship androgens/estrogens and not with the absolute quantity of hormones implicates a regulatory process that makes relative hormonal action change.

Men in general have a lesser 2D: 4D relationship in women than in all the ethnic groups. The effect is much more intense in the right hand than in the left⁵⁹. The male/female hormone differences change said relationship in a measurable factor of sexual dimorphism. Since the stages in which the growth of the fingers depends on the amount of receptors is the same as the amount of receptors are the same as the sexual steroids that masculinize or feminize the brain, the relationship 2D:4D is a marker, easy to quantify, of the cerebral dimorphism that are due to prenatal androgen exposure⁶⁰.

In the adult stage of life, the relationship does not change⁶¹, although the fingers grow.

Several data support this parameter is effectively a marker of the prenatal exposure to androgens. Women that suffer congenital adrenal hyperplasia, because of strong prenatal exposure to androgens deriving from the adrenal glands, possess a low relationship and presents homosexuality or bisexuality, directly related to the degree of exposure⁶². This relationship is also related with sensibility to testosterone in male-to-female transsexual people⁶³.

Statistically significant characters have been studied in males and females heterosexuals and homosexuals. The analysis in adults of the features of hands has shown⁶⁴ that

⁵⁸ Zheng, Z., Cohn, M.J. "Developmental basis of sexually dimorphic digit ratios". *Proceedings of the National Academy of Sciences of the United States of America* 108, 2011, 16289-16294.

⁵⁹ Manning, J.T., Churchill, A.J., Peters, M. "The effects of sex, ethnicity, and sexual orientation on self-measured digit ratio (2D:4D)". *Archives Sexual Behavior* 36, 2007, 223-233.

⁶⁰ Berenbaum, S.A., Bryk, K.K., Nowak, N., Quigley, C.A., Moffat, S. "Fingers as a marker of prenatal androgen exposure". *Endocrinology* 150, 2009, 5119-5124.

⁶¹ Talarovicová, A., Krsková, L., Blazeková, J. "Testosterone enhancement during pregnancy influences the 2D:4D ratio and open field motor activity of rat siblings in adulthood". *Hormones Behavior* 55, 2009, 235-239.

⁶² Brown, W.M., Hines, M., Fane, B.A., Breedlove, S.M. «Masculinized finger length patterns in human males and females with congenital adrenal hyperplasia» *Hormones Behavior* 42, 2002, 380-386. Okten, A., Kalyoncu, M., Yariş, N. «The ratio of second- and fourth-digit lengths and congenital adrenal hyperplasia due to 21-hydroxylase deficiency». *Early Human Development* 70, 2002, 47-54.

⁶³ Green, R., Young, R. «Fingerprint asymmetry in male and female transsexuals». *Personality and Individual Differences* 29, 2000, 933-942.

⁶⁴ Martin, J.T., David, A., Puts, S., Breedlove, M. «Hand asymmetry in heterosexual and homosexual men and women: relationship to 2D:4D digit ratios and other sexually dimorphic anatomical traits». *Archives of Sexual Behavior* 37, 2008, 119-132. Lalumiere, M. L., Blanchard, R., Zucker, K. J. «Sexual orientation and handedness in men and women: A meta-analysis». *Psychological Bulletin* 126, 2000, 575-592.

homosexual women showed the same pattern of asymmetry than male heterosexuals. The pattern consisted in the differences of the value of the relationship 2D:4D (second to fourth digit ratio) depending if the asymmetry is on the right or on the left. However, the difference according to the directional asymmetry was not observed in heterosexual women or in homosexual men.

It has recently been described⁶⁵ that the administration of testosterone to young girls reduces the capacity of empathetic knowledge typically feminine and in parallel a modification of the asymmetry towards the right in the relationship 2D:4D. There is, therefore, a masculinization of the patterns in homosexual women.

The effect of the exposure to sexual steroids, during late childhood and the termination of growth during adolescence, it seems to be mediated by the type of androgen receptor, of high or low efficiency⁶⁶.

In such a way then that the scenario⁶⁷ of the homosexuality predisposition seems to go through the genetic inheritance of two varieties of androgen receptors, as we have suggested. Male homosexuality would be predisposed by low sensibility to androgens, and in women, an excess of exposure would potentiate a masculinization of the patterns, in the prenatal stage. These observations cannot be attributed to perceptions or conduct. The first component of feeling male or female is established in children at the age of two and a half years. At this age, identity is separated from sexuality that appears later on.

3. Sexual dimorphism in some brain structures and functions

It is known that the structure of interconnections between diverse areas of the brain, the size of some regions, and some skills are different in males and females. The advancement of a couple of years of `puberty in girls with respect to boys makes the hormones act modulating a cerebral organization with a feminine pattern or with a masculine pattern, consolidating the innate patterns⁶⁸.

These characteristics of one or the other sex that is indicated hereafter do not correspond to the areas and the connections directly implicated with the sexual brain, nor to the parameters of response to the sexual stimuli. However, differences are shown in

⁶⁵ Van Honk, J., Schutter, D.J., Bos, P.A., Kruijt, A.W., Lentjes, E.F., Baron-Cohen, S., «Testosterone administration impairs cognitive empathy in women depending on second-to-fourth digit ratio». *Proceedings of the National Academy of Sciences of the United States of America* 108 (8), 2011, 3448-3452.

⁶⁶ Manning, J.T. et al. «The second to fourth digit ratio and variation in the androgenreceptor gene». *Evolution and human Behavior* 24, 2003, 399-405. Malas, M.A., Dogan, S., Evcil, E.H., Desdicioglu, K. «Fetal development of the hand, digits and digit ratio (2D:4D)» *Early Human Development* 82, 2006, 469-475. Lutchmaya, S., Baron-Cohen, S., Raggatt, P., Knickmeyer, R., Manning, J.T. «2nd to 4th digit ratios, fetal testosterone and estradiol». *Early Human Development* 77, 2004, 23-28.

⁶⁷ Breedlove, S.M. «Minireview: Organizational hypothesis: Instances of the fingerpost». *Endocrinology* 151, 2010, 4116-4122.

⁶⁸ Bramen, J.E., Hranilovich, J.A., Dahl, R.E., Forbes E.E., Chen, J., Toga, A.W., Dinov, I.D., Worthman, C.M., Sowell, E.R. «Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity». *Cerebral Cortex* 21(3), 2010, 636-646. Blakemore, S.J. et al. «The role of puberty in the developing adolescent brain». *Human Brain Mapping* 31, 2010, 926-933.

homosexual people with the general differences of people of their same sex. As is to be expected, since the differences of the male brain and the female brain present the corresponding dimorphisms to the action of hormones that is consolidated with the experiences and ways of life.

3.1 Hemispheric asymmetry

Generally, it is widely accepted that brain asymmetry, whose spatial direction varies according to the area, is more pronounced in males than in females⁶⁹, especially towards the right.

Studies carried out with volunteers with different sexual orientation⁷⁰ have revealed that heterosexual males and homosexual females have brain asymmetry towards the right, while the volumes of the brain hemisphere were symmetric in homosexual males and heterosexual women. These differences of asymmetric hemispheres can reflect that the connections between the hemispheres are more pronounced in female heterosexuals and male homosexuals. This has been pointed out⁷¹, as the functions of the two hemispheres are not so intensely different in females, whatever their sexual orientation is.

It is of interest the fact of the different concentration of androgen receptors in the two hemispheres⁷².

3.2 Differences in the size of areas

The hippocampus, a region completely implicated in the processes of learning and memory, is of greater volume as general rule in the female than in males⁷³. They contain more quantity of estrogen receptor⁷⁴, although the posterior part also sensible to testosterone.

⁶⁹ Toga, A.W., Thompson, P.M. «Mapping brain asymmetry». *Nature Review Neuroscience* 4, 2003, 37–48. Good, C.D., et al. «Cerebral asymmetry and the effects of sex and handedness on brain structure: A voxel-based morphometric analysis of 465 normal adult human brains». *Neuroimage* 14, 2001, 685–700. Luders, E., et al. «Hemispheric asymmetries in cortical thickness. *Cerebral Cortex* 16, 2006, 1232–1238. McCormick, C.M., Witelson, S.F. «Functional cerebral asymmetry and sexual orientation in men and women». *Behavior Neuroscience* 108, 1994, 525–531.

⁷⁰ Savic, I., Lindstrom, P. «PET and MRI show differences in cerebral asymmetry and effects of sex and functional connectivity between homo- and heterosexual subjects». *Proceedings of the National Academy of Sciences of the United States of America* 105(27), 2008, 9403–9408. Rahman, Q., Cockburn, A., Govier, E. «A comparative analysis of functional cerebral asymmetry in lesbian women, heterosexual women, and heterosexual men». *Archives of Sexual Behavior* 37(4), 2008, 566–571. McCormick, C.M., Witelson, S.F. «Functional cerebral asymmetry and sexual orientation in men and women.» *Behavior Neuroscience* 108, 1994, 525–531.

⁷¹ Zaidel, E., Aboitiz, F., Clarke, J. «Sexual dimorphism in interhemispheric relations: anatomical-behavioral convergence». *Biological Research* 28, 1995, 27–43. Allen, L.S., et al. «Sex differences in the corpus callosum of the living human being». *Journal of Neuroscience* 11, 1991, 933–942.

⁷² Sholl, S.A., Kim, K.L. «Androgen receptors are differentially distributed between right and left cerebral hemispheres of the fetal male rhesus monkey». *Brain Research* 516, 1990, 122–126.

⁷³ Goldstein, J.M., Seidman, L.J., Horton, N. J., Makris, N., Kennedy, D.N., Caviness, V.S.Jr., Faraone, S.V., Tsuang, M.T. «Normal sexual dimorphism of the adult human brain assessed by *in vivo* magnetic resonance imaging». *Cerebral Cortex* 11, 2001, 490–497.

⁷⁴ Morse, J.K., Scheff, S.W., DeKosky S.T. «Gonadal steroids influence axon sprouting in the hippocampal dentate gyrus: a sexually dimorphic response». *Experimental Neurology* 94, 1986, 649–658. Rahman, Q., Abrahams, S., Wilson, G.D. «Sexual-orientation-related differences in verbal fluency». *Neuropsychology* 17, 2003, 240–246. Wegesin, D.J. «Relation between language lateralisation and spatial ability in gay and straight women and men». *Laterality* 3, 1998, 227–239.

3.3 Functional connections and response to stimuli.

The cerebral amygdale has a key role in the emotional reactions to external stimuli, when the biological sense of emotions is evaluated inciting the diverse sensorial stimuli. The amygdaloid complex is in charge of processing emotions and associating them to cognitive and motivational processes. It contains a great number of androgen receptors that play a critical role in the development and maintenance of dimorphism in the adult⁷⁵. It is differentially activated in both sexes⁷⁶ and the function of the left and of the right in the processing of the emotional memory differs in women and men⁷⁷. Women activate the left and males the right. Hence, these differences, depending on the sex, in the emotional evolution of the sensorial stimuli underlying the diverse strategies in tasks that have no direct relation with sexual activity.

It carries out dimorphic connections with other cerebral structures, such as the subcallosa region and the anterior cingulated cortex implicated in the mediation of the state of mind and the processes related with anxiety⁷⁸. Homosexuals showed connections with the amygdale atypical for their sex. In homosexual male and heterosexual females, the connections of the left amygdale were more intense in homosexual females and in heterosexual men. Also in homosexual females and heterosexual males, the connections are established with the caudate nucleus, the putamen and the prefrontal cortex, while in homosexual males and in heterosexual females, the connections are mainly between the contra-lateral amygdale and the anterior cingulated cortex.

The differences of the connections that the brain amygdale establishes with other areas in women and in men explains the affective disorders with 2-3 times more frequency in women than in men, and the close functional connections between the amygdale and the cingulate cortex in women it is assumed to be a possible neurobiological substrate of their greater vulnerability⁷⁹. It is significant, in this sense, in this regard that the incidence of depression and suicidality is higher in homosexuals, particularly in males⁸⁰, without it having any kind of relationship with the climate of tolerance or intolerance to homosexuality in which it develops⁸¹.

⁷⁵ Cooke, B.M. «Steroid-dependent plasticity in the medial amygdala». *Neuroscience* 138, 2006, 997-1005.

⁷⁶ Stanton, S.J., Wirth, M.M., Waugh, C.E., Schultheiss, O.C. «Endogenous testosterone levels are associated with amygdala and ventromedial prefrontal cortex responses to anger faces in men but not women». *Biological Psychology* 81, 2009, 118-122.

⁷⁷ Hamann, S. «Sex differences in the responses of the human amygdala». *Neuroscientist* 11, 2005, 288-293.

⁷⁸ Phillips, M.L., et al. «Neurobiology of emotion perception II: Implications for major psychiatric disorders». *Biological Psychiatry* 54, 2003, 515-528.

⁷⁹ Wang, J., et al. «Gender difference in neural response to psychological stress». *Social cognitive and affective neuroscience* 2, 2007, 227-239.

⁸⁰ Fergusson, D.M., Horwood, L.J., Beautrais, A.L. «Is sexual orientation related to mental health problems and suicidality in young people?» *Archives of General Psychiatry* 56, 1999, 876-880. Wang, J., et al. «High prevalence of mental disorders and co-morbidity in the Geneva Gay Men's Health Study» *Social psychiatry and psychiatric epidemiology* 42

⁸¹ d Sandfort, T.G. M., ten Have, M. «Suicidality and sexual orientation: Differences between men and women in a general population-based sample from The Netherlands». *Archives of Sexual Behavior* 35, 2006, 253-262.

Other interactions between areas also show differences. For example, the sensorimotor cortex and the striated body show stronger connections in homosexual women and heterosexual women. These regions have been associated with the interest to act in the external environment, such as the reactions of struggle and flight, statistically more common in males⁸².

The inhibition factor of the startle response or *pre-pulse inhibition* factor refers to the reduction of the startle response to a strong sensorial stimulus when that stimulus has been preceded by a weak stimuli and it reflects an innate mechanism of the sensorimotor input. Women display a lesser value than males⁸³.

Startle response has also been examined in to auditory stimuli in heterosexual and homosexual males and females⁸⁴. Female homosexuals showed a value of this masculinized factor compared with other females; to the contrary, in males there were no differences, but that they exhibited typically masculine patterns.

3.4 Dimorphic abilities

Differences have been described, statistically significant, between males and women in some characteristics. They deal with properties and human capabilities that are learnt and developed with practice and are sustained with a natural innate predisposition linked to the genetic sex. The predominant abilities in one or the other sex reflect the diverse cognitive and emotional strategies of the male and the woman to process the stimuli and respond to them. Brain plasticity is very intense and being that they are all human abilities, each person potentiates and harmonizes to reach their own plenitude.

Various studies seem to indicate that in general homosexual people show the opposite profile to their sex in verbal fluency or in spatial orientation tasks⁸⁵. Some activities in which the males generally reach better marks -as in visuospatial orientation- the scores that women reached depended on the state of their menstrual cycle⁸⁶. Moreover, it increased with the administration of testosterone⁸⁷.

In summary, the brain structure occurs during fetal life and infancy, and consolidates its

⁸² Klein, L.C., y cols., op.cit. Korte, S.M., et al. «The Darwinian concept of stress: Benefits of allostasis and costs of allostatic load and the trade-offs in health and disease». *Neuroscience and Biobehavioral Reviews* 29, 2005, 3–38.

⁸³ Rahman, Q., Kumari, V., Wilson, G.D. «Sexual orientation-related differences in prepulse inhibition of the human startle response behavioral». *Neuroscience* 117, 2003, 1096–1102.84 .

⁸⁴ Mcfadden, D., Pasanen, E.G. «Comparison of the auditory systems of heterosexuals and homosexuals: Click-evoked otoacoustic emissions». *Proceedings of the National Academy of Sciences of United States of America* 95, 1998, 2709–2713.

⁸⁵ Rahman, Q., Abrahams, S., Wilson, G.D. «Evidence continues to accumulate about the biological orientation related differences in verbal fluency». *Neuropsychology* 17, 2003, 240–246. Rahman, Q., Wilson, G.D. «Large sexual-orientation-related differences in performance on mental rotation and judgment of line orientation tasks». *Neuropsychology* 17, 2003, 25–31. Wegesin, D.J. «Relation between language lateralisation and spatial ability in gay and straight women and men» *Laterality* 3, 1998, 227–239.

⁸⁶ Gizewski, E.R., Krause, E., Wanke, I., Forsting, M., Senf, W. «Gender-specific cerebral activation during cognitive tasks using functional MRI: comparison of women in mid-luteal phase and men». *Neuroradiology* 48, 2006, 14–20.

⁸⁷ Aleman, A., Bronk, E., Kessels, R.P., Koppeschaar, H-P, von Honk, J. "A single administration of testosterone improves visuospatial ability in young women". *Psychoneuroendocrinology* 29, 2004, 612-617.

specific sexual pattern beginning at puberty and goes on throughout adolescence. The atypical sexual parameters so much so in the asymmetries as in the functional connections of homosexual subjects cannot be attributed only to learnt effects or of the chosen options, but that suggest a bond with neurobiological entities. The asymmetry patterns and some aspects of dimorphism are detected in infancy. Brain maturity continues during adolescence, especially in boys⁸⁸ providing a substrate for environmental and social factors.

The cause, even though it can be multifactorial, essentially includes the interaction between prenatal and postnatal testosterone and the variants of androgen receptors. The genetic factor is more potent in male homosexuality than in female⁸⁹.

It poses, therefore, the importance of the education in abilities, tastes, emotiveness, sensibility, affectivity, sexuality, etc. Hormones modify the form that tasks undertake⁹⁰ and the lived experiences and the generation of abilities during development and schooling influence in the development of the neural substrates that underlie the acquired skills. An example of this would be verbal fluency with the differential reinforcement of language comprehension.

Like other characteristics, sexual orientation is not “a continuo between two extremes”, that is concretized in one sense or other merely by environmental influences, or purely indifferent options⁹¹. It is a fact the existence of an innate predisposition of the mechanisms that underlie male homosexuality, and it is a fact too that it is not a determinant, but that it consolidates or dilutes with lived experiences in these crucial stages of infancy and adolescence. Only by keeping this in mind, will it be possible for people to make freely a decision of utmost importance in their lives.

4. Dimorphism of the sexual brain

4.1 Activation in puberty of the areas of the sexual brain

The circuit implicated in the response to sexual stimuli is mainly formed by the hypothalamus and the brain amygdale that form part of the limbic system. The central layer of the brain and regulated by the frontal lobe in the brain cortex. These areas are related between themselves by a great fascicle, a set of neuronal fibers, in the midbrain, where the principal centers responsible for brain systems of reward or punishment are found.

The hypothalamus forms part of the limbic system and coordinates body expression of the emotional states; it is a coordinating center of responses so much somatic as autonomous or

⁸⁸ Paus, T. «Mapping brain maturation and cognitive development during adolescence» *Trends in Cognitive Science* 2005, 60–68.

⁸⁹ Lyons, M.J., et al. «A twin study of sexual behavior in men» *Archives of Sexual Behavior* 33, 2004, 129–136.

⁹⁰ Hausmann, M.M., Bayer, U. «Armonía hormonal». *Mente y Cerebro* 50, 2011, 70.

⁹¹ Ellis, L., Burke, D., Ames, M.A. «Sexual orientation as a continuous variable: a comparison between the sexes». *Archives of Sexual Behavior* 16, 1987, 523–529.

vegetative. Thus, it is the main regulatory center to sexual stimuli response. The brain amygdale evaluates the stimuli in relations with its biological sense and is tinged as award or punishment. At the same time as the hippocampus, also part of the limbic system, stores the emotional memories, tinted as positive or negative ones.

In human beings, the reciprocal connections of the hypothalamus and the limbic system, with the brain cortex provokes that the emotional states become conscious generating emotions and permitting that instinctive behavior be transformed in conduct.

The differences of the sexual brain in men and women are organized during embryonic development, but it is only activated in adolescence and in a differentiated form due to the exposure to the circulating hormones of puberty. Adolescence conveys emotional, psychological, social, mental, and physical changes in growth⁹². An increase interest for sexual activity⁹³ takes place as do changes in motivation.

Hormonal levels boost the functionality of the areas of greater concentration of their receptors. The concentration of the receptors of estrogens is regulated by the modification that the estrogen realizes on the expression of the gene that they encode⁹⁴.

4.2 Hypothalamus

By action of the sexual hormones in the development of the hypothalamus, the brain becomes receptive to sexual stimuli⁹⁵, since it has the cores that process sexual behavior. It consists of a series of cores that are localized from the part most anterior to the posterior, two of them correspond to the anterior zone the NIHA1 and the NIHA2, another two to the region caudal, the NIHA3 and NIHA4 and others in the zone media posterior, the medial mammillary nucleus and the lateromamilar.

Estrogen receptors⁹⁶ are present in different concentrations, depending on the sex, along the hypothalamus from the frontal zone, rostral, towards the caudal zone, the nape, in the previous areas. Androgen receptors in the hypothalamus are also found distributed in a different form in men and women⁹⁷, in males they are more abundant in the mid zones and in the posterior ones⁹⁸.

⁹² Schulz, K.M., Molenda-Figueira, H.A., Sisk, C.L. «Back to the future: The organizational- activational hypothesis adapted to puberty and adolescence». *Hormones and Behavior* 55, 2009, 597-604.

⁹³ Sisk, C.L., Zehr, J.L. «Pubertal hormones organize the adolescent brain and behaviour». *Frontiers in Neuroendocrinology* 26, 2005, 163-174.

⁹⁴ Nugent, B.M., Schwarz, J.M., McCarthy M.M. «Hormonally mediated epigenetic changes to steroid receptors in the developing brain: Implications for sexual differentiation». *Hormones and Behavior* 59, 2011, 338-344.

⁹⁵ Hulshoff Pol, H.E., Cohen-Kettenis, P.T., Van Haren, N.E.M., Peper, J.S., Brans, R.G.H., Cahn, W., Schnack, H.G., Gooren, L.J.G., Kahn, R.S. «Changing your sex changes your brain: influences of testosterone and estrogen on adult human brain structure». *European Journal of Endocrinology* 155, 2006, s107-s114.

⁹⁶ Kruijver, F.P.M., Balesar, R., Espila, Unga, A.M., Unmehopa, A., Swaab, D.F. «Estrogen Receptor Distribution in the Human Hypothalamus in Relation to Sex and Endocrine Status». *Journal of Comparative Neurology* 454, 2002, 115-139. Ishunina, T.A., Swaab, D.F. «Estrogen receptor-alpha splice variants in the human brain». *Gynecological Endocrinology* 24, 2008, 93-98.

⁹⁷ Fernández-Guasti, A, Kruijver F.P.M., Fodor, M., Swaab, D.F. «Sex differences in the distribution of androgen receptors in the human hypothalamus». *Journal of Comparative Neurology* 425, 2000, 422-435.

⁹⁸ Fernández-Guasti, *op.cit.* 96.

Several studies, classic already, showed differences of size between heterosexual and homosexual males that continue requiring confirmation⁹⁹. However, the question of size is not a defined and definite parameter since it can be affected by multiple factors dependent on the forms of life.

4.3 Brain amygdale

The brain amygdale, or amygdaloid complex, is a functional unit of areas perfectly interconnected. The neurons of each nucleus permit the input and output of sensorial information. In turn, they connect between themselves in the amygdaloid complex; the central nucleus of the amygdale is composed principally by inhibiting neurons, brakes to the step of the entering or the exiting information, which establish functional microcircuits exercising the control of the acquisition and regulation of the conduct, as has been widely investigated with the medium¹⁰⁰. Apart from the functions already cited, contrasts the difference of sex in the response to sexual stimuli, especially visual ones, very intense in males¹⁰¹.

Its strategic location, in the frontal part of the temporal lobe, permits it to act as a call for attention center over the new, emotional, or important of sensorial information. The brain amygdale translates the sensorial, the stimulus, to emotion in the spectrum of basic emotions.

How does the amygdale evaluate sexual stimuli? As with any other stimulus, the signals pass from the processing areas of the sensorial brain directly to the amygdale and in these structures, the communication is elaborated after a series of enquiries to several centers.

Its connection with the ventral striatum, that forms part of the reward system, identifies the award. It evaluates the reward or punishment connected with the frontal lobe implicated in knowledge, the memory, and the conscience. Therefore, the amygdale guides the behavior based on the reward that it processes; its connection with the orbito-frontal cortex integrates the emotional and cognitive information and “calculates in real time” the rewarding value of the stimulus. It increases the affective significance of a stimulus, with a similar effect to an increase in attention and motivation.

In relation to what does the award measure and conform to a feeling of attraction or

⁹⁹ LeVay, S. «A difference in hypothalamic structure between heterosexual and homosexual men». *Science* 253, 1991, 1034–1037. Swaab, D.F., Hofman, M.A. «An enlarged suprachiasmatic nucleus in homosexual men». *B in the human brain*. *Proceedings of the National of Academy of Sciences of United States of America* 89, 1992 *Brain Research* 537, 1990, 141–148. Allen, L.S., Gorski, R.A. «Sexual orientation and the size of the anterior commissure, 7199–7202. Byne, W., Lasco, L.B., Shinwari, A., Edgar, M.A., Morgello, S., Jones, L.B., Tobet, S. «The interstitial nuclei of the human anterior hypothalamus: an investigation of sexual variation in volume and cell size, number and density». *Brain Research* 856 (1-2), 2000, 254–258.

¹⁰⁰ Sprengel, R., Deisseroth, K., Stadler, M.B., Muller C., Luthi, A. «Encoding of conditioned fear in central amygdale inhibitory circuits» *Nature* 277, 2010, 277-284. Haubensak, W., Kunwar, P.S., Ciochi, C., Wall, H.N., Ponnusamy, R. S., Biag, J., Dong, H-W., Deisseroth, K., Callaway, E.M., Fanselow, M.S., Luthi, A., Anderson, D.J. «Genetic dissection of an amygdale microcircuit that gates conditioned fear» *Nature* 468, 2010, 270-277.

¹⁰¹ Hamann, S. *Op. cit.* 76. Hamann S, Herman R, Nolan C, Wallen K. «Men and women differing in amygdala response to visual sexual stimuli» *Nature Neuroscience* 7, 2004, 411–416.

rejection?

Emotional stimuli set off changes in our body. Information on these types of body reactions are remitted once again to the brain, the amygdale complex, through intermediate stations and that later on are stored in the anterior insula, as a species of subjective feeling. In this secondary representation in the insula the faculty of perceiving consciously our emotional states and talking about them would be based.

Check the evaluation of the value of a reward in relation with the biological function of the stimulus. When the brain amygdale is activated with the arrival of the processed stimulus “calmly” activates the endocrine system of the hypothalamus that liberates hormones and activates the autonomous nervous system in the brain stem. What is generated viscerally is associated and it habitually corresponds in each case with the trigger situation.

In general, and by cerebral design, feminine strategies permit for a greater participation of emotion in the cognitive processes. The cerebral amygdale implicated in the formation of the emotional memory¹⁰², the processing of the emotional memory is different in males and in females¹⁰³. The amygdale, situated in front of the hippocampus in the depth of the temporal lobe, participates in the response to sexual stimuli in a different manner in both sexes. In males, the amygdale has more connection with the hippocampus while in females there is a greater orbito-frontal cortex/amygdale connection, what signifies a greater capacity to control the answers than in males.

5. Neuronal processing dynamics of sexual conduct

The studies of brain dynamics, measuring the emotions brought about, show the patterns of differential activation according to sex in response to sexually exciting stimuli. At the same time, the type of stimulus used to know male/female differences in the response to those stimuli have been used to know the dynamics of homosexual orientation in comparison with heterosexual orientation. The stimulus that most significantly contrasts the response of the woman and the man is the visual. Hence, it also offers more possibilities for the investigation.

The study of rat amygdale lesions has highlighted a fundamental distinction between the role of the human amygdale in the called appetitive sexual conduct sexual and consummatory. This is the desire, the motivation to obtain sexual recompense and the achievement of that response. The lesions in the amygdale medial affect the capacity of male rats to respond the sexual signals of a receptive female, that is to say it annuls sexual appetite¹⁰⁴.

¹⁰² Cahill, L., Haier, R.J., White, N.S., Fallon, J., Kilpatrick L, Lawrence C, et al. «Sex-related difference in amygdala activity during emotionally influenced memory storage». *Neurobiology Learning and Memory* 75, 2001, 1–9. Cahill, L. Desmond, J.E., Zhao, Z., Gabrieli, J.D.E. «Sex differences in the neural basis of emotional memories». *Proceedings of the National Academy of Sciences of the United States of America* 99, 2002, 10.789–10.794; Cahill, L., Uncapher, M., Kilpatrick, L., Alkire, M.T., Turner, J. (2004) «Sex related hemispheric lateralization of amygdala function in emotionally influenced memory: an fMRI investigation». *Learning & Memory* 11, 261–266

¹⁰³ Hamann, S. *Op. cit.* 76

¹⁰⁴ Everitt, B.J. «Sexual motivation: a neural and behavioral analysis of the mechanisms underlying appetitive and copulatory responses of male rats». *Neuroscience and Biobehavioral Reviews* 14, 1990,

5.1. Motivation

Men and women differ in the motivation responses to erotic visual stimuli. Men are more physiological and psychological sensitive to sexually exciting visual stimuli and show greater motivation to find and interact with such stimuli.

Studies of neuroimaging¹⁰⁵ have researched that if the amygdale plays a key role in the mediation of the emotional responses to erotic visual stimuli in a different manner in men and in women. The hypothesis of the starting point, that has been able to affirm by studies from different teams, posed that the differences between man and women in the mode of processing the visual stimuli -the specific activation of brain areas- arise from the differences in the cognitive styles and of sexual practices, while the excitation does not change because of it. If it were so, al equate genital excitation provoked by erotic sexual stimuli, the response processing should differ¹⁰⁶.

Sexual visual stimuli were carefully preselected -diverse types of photographs and videos- to guarantee the coincidence of men and women regarding the level of excitation. The measures of genital excitement have limitations such as the bias of volunteers and the differences of the system of measuring it for each sex. However, as has been mentioned, very recently Rieger and Savin-Williams have substituted them by the simple measure of the pupil's dilation, and has thus confirmed prior information and has surpassed the limitations¹⁰⁷.

Men showed a significant greater activation than women to sexual stimuli did, especially in the left amygdale and the hypothalamus that receives the evaluated information and transfers them to the specific nuclei of the sex of the hypothalamus. This matches with the results of previous studies with rats that implicate the amygdale in male sexual motivation. It is coherent with the results of other studies of neuroimaging that implicated the human amygdale in other forms of incentive motivation, for example, the desire for food, or for drugs¹⁰⁸.

The “neutral” stimuli produce similar responses for women and men.

On the contrary, surprisingly, in women there are no zones of greater activation for the sexually exciting stimuli. The answers are not in women, in difference with the males. So influenced by the degree of eroticism of the stimuli, but that depends more on other non-

217–232.

¹⁰⁵ Hamann, S., *Op. cit.* 100. Hamann, S., Canli, T. «Individual differences in emotion processing». *Current Opinion Neurobiology* 14, 2004, 233–238.

¹⁰⁶ Hamann, S. *op. cit.* 76.

¹⁰⁷ Rieger, G., Savin-Williams R.C. “The Eyes Have It: Sex and Sexual Orientation Differences in Pupil Dialtion Patterns”.

PLoS ONE 7, 2012, e40256. Cited in 7.

¹⁰⁸ Arana, S.F., Parkinson, J.A., Hinton, E., Holland, A., Owen, A.M. «Dissociable contributions of the human amygdala and orbitofrontal cortex to incentive motivation and goal selection». *Journalof Neuroscience* 23, 2003, 9632–9638. Gottfried, J.A., O’Doherty, J., Dolan, R. J. «Encoding predictive reward value in human amygdala and orbitofrontal cortex». *Science* 301, 2003, 1104–1107.

sexual aspects of the stimulus, as is the context¹⁰⁹.

In women, emotional memory is very intense; memories with a positive or negative emotional load are stored in the hippocampus, once they have been evaluated by the brain amygdale and contextualized¹¹⁰.

In summary, sexual excitement is activated in the cognitive and physiological processes that eventually can lead to a sexual behavior. In the case of humans apart from depending on genetic and hormonal factors, depending on the sensorial and cognitive brain dynamic and of the complex influences of experiences and context¹¹¹.

5.2 Consummation

In the processing of the consummatory conduct, sexual pleasure, the brain amygdale, sexual pleasure, the brain amygdale also has a differential function. In males, activity in one area, the left amygdale¹¹², is reduced in concordance with studies on animals. With physical contact, in the male brain the system of rewards -especially ventral tegmental area that synthesizes dopamine and the nucleus *accumbens* that receives it and projects it to the cortex- finds itself active bind to ejaculation. The brain has also increased the activity in the regions that participate in the plastic memories and in vision, as well as the cerebellum that coordinates movement, and collaborates in emotions.

On the contrary, in organism the female brain diminishes the activity of the left orbito-frontal region responsible for the control of impulse and self-control, the dorso-medial and prefrontal cortex. It is the cortical inactivity and the silencing of the amygdale what triggers the dopamine wave, the situation of pleasure that makes it receptive.

The response of both in the consummatory male/female relationship is synchronized, asymmetrically and complementary. It is directly associated with the personal transmission of life.

5.3 Evolution of sexuality

The great majority of people have a heterosexual sexual orientation¹¹³ throughout all of their life. This results in the complementarity and asymmetry of the corporal relationship

¹⁰⁹ Peplau, L.A. «Human sexuality: How do men and women differ?» *Current Directions in Psychological Science* 12, 2003, 37–40. Rupp, H.A., Wallen, K. «Sex differences in response to visual sexual stimuli: A review». *Archives of Sexual Behavior* 37,2008, 206-218.

¹¹⁰ Cahill, L., *op. cit.* 101. Canli, T., Desmond, J.E., Zhao, Z., Gabrieli, J.D.E. «Sex differences in the neural basis of emotional memories». *Proceedings of the National Academy of Science of the United States of America* 99, 2002, 10789–10794. Canli, T., Zhao, Z., Brewer, J., Gabrieli, J.D.E., Cahill, L. «Event-related activation in the human amygdala associates with later memory for individual emotional experience». *Journal of Neuroscience* 20, 2000, 1–5.

¹¹¹ Schober, J.M., Pfaff, D. «The neurophysiology of sexual arousal». *Best Practice and Research Clinical Endocrinology and Metabolism* 21, 2007, 445–461.

¹¹² Holstege, G., Georgiadis, J.R., Paans, A.M.J., Meiners, L.C, van der Graaf, H.C.E., Reinders, T.S.. «Brain activation during human male ejaculation». *Journal of Neuroscience* 23, 2003, 9185–9193. Stachira, E. «El orgasmo en el cerebro». *Mente y Cerebro* 44, 2010, 65-69.

¹¹³Savin-Williams, R.C., Joyner, K., Rieger, G. "Prevalence and stability of self-reported sexual orientation identity during young adulthood." *Archives of Sexual Behavior* 41, 2012, 103-110.

between people of a different sex allows for the transmission of life.

It is obvious that in the animal world/sexual instinct did not evolve to satisfy pleasure but to impulse and assure reproduction; thus satisfaction of the instinct involves situations that orient and direct in a *determined y decisive* form the behavior to the precise objective for reproduction.

As what happens with everything that is human, the specific attraction between a man and a woman, in a personal manner, sinks the roots in this biological background that permits the transmission of life. The brain codes, where some concrete neuronal structures participate generate neurotransmitters and neurohormones that activate in certain situations and thus predispose the behavior towards its objective, but it does not determine it.

In fact, the concentration of the hormones in blood significantly rises during the copula and in a sexually dependent form. In men the vasopressin increases -hormone of the masculine energies- in the previous phase to the union, to liberate later on oxytoxin - hormone of confidence- women only liberate oxytoxin. In turn, the corporal union permits an exchange of hormones: in women testosterone increases which keeps her receptive during a longer period and in men it decreases and the prolactin maintaining the feeling of unity in the time of refractory. Only in this precise and universal manner, not cultural, the union of the personal bodies of one and the other makes them capable of personally transmitting human life. Only the union of two personal bodies of the opposite sex initiates the neuronal circuits towards the consummation of sexual attraction that opens the paternal/maternal-filial relationship.

The asymmetry of sexual behavior of both sexes sinks its roots in the biological level that pursues the reproductive efficiency to which the transmission of life is bound¹¹⁴.

6. Heterosexual , homosexual and bisexual orientation in men and women

The study of the response pattern to sexual stimuli requires analyzing the emotions aroused and measuring genital excitation.

Numerous papers have been carried out with diverse groups of people of different sex and sexual orientation and having as stimulus the visualization of photographs and videos with erotic content. In others, the smell of derived feminine hormones or masculine present in the sweat of men, or the emotion aroused by the sight of female or male faces have been used.

The information, in its entirety, does not contradict each other, although the values are not statistically significant, due to the difficulty of purely profiling the sexual orientation of the volunteers and due to the difficulties, already mentioned of measuring excitation. However, as has been commented beforehand, the pupil dilation parameter autonomic, unconsciously

¹¹⁴ Baumeister, R.F. «Gender differences in erotic plasticity: The female sex drive as socially flexible and responsive». *Psychological Bulletin* 126 (3), 2000, 347-374

and not modifiable manner reflects the invasive character of the genital measurements¹¹⁵.

The scenario produced by the results is the following:

- 1) As a reflex of the general difference in masculine and feminine sexuality, the relationship between genital excitation and masculine or feminine sexual stimuli, is considerably stronger in men than in women¹¹⁶ in such a way that male heterosexuals are exclusively to men who are attracted to women, while homosexual men are almost exclusively attracted to men. Hence, there exist very few spontaneous bisexuals. In general terms, for males the pattern of motivation, desire is relatively constant in time and in different situations. This shows the innate predisposition of the patterns.
- 2) On the contrary, heterosexual women respond with the basic weak genital excitation, and in a similar manner, for both sexes. Homosexual women respond more before women; the same as males respond more strongly to stimuli of the same sign as their orientation. This is, in women homosexuality appears, rather, as a certain masculinization in the response to stimuli. There does not exist, an innate genetic predisposition as occurs with males and spontaneously results in bisexuals.

Be the sexual orientation whatever it is, feminine sexuality more than male sexuality, is flexible, and its receptivity, to respond to masculine sexual behavior, makes it to a certain extent adaptable to changing circumstances. By which women are not spontaneously only homosexuals but bisexuals. Some heterosexual women have sexual relations with people of the same sex, in a sporadic form.

This is to say, there exists a substantial difference between the sexes in the organization of sexual orientation.

6.1 *Response to visual sexual stimuli according to sexual orientation*

Explicit visual sexual stimuli generate in men more response than in women, with a more intense activation of the amygdale and the hypothalamus¹¹⁷.

Several studies used videos with heterosexual content, with scenes of a man and a woman, and of homosexual content, with a couple of the same sex. The results of the analysis of functional image, when measuring the emotion brought about by the stimuli, showed that sexual arousal was dependent on the type of stimulus and the response of the brain of male heterosexuals to heterosexual stimuli is comparable to that of male homosexuals to homosexual stimuli¹¹⁸. On the contrary, the response of the brain to stimuli of the opposite

¹¹⁵ Bradley, M.M., Miccoli, L., Escrig, M.A., Lang, P.J. «The pupil as a measure of emotional arousal and autonomic activation». *Psychophysiol-ogy* 45, 2008, 602–607. Heaver, B., Hutton, S.B. «Keeping an eye on the truth? Pupil size changes associated with recognition memory». *Memory* 19, 2011, 398–405

¹¹⁶ Chivers, M.L., Rieger, G., Latty, E.M., Bailey, J.M. «A sex difference in the specificity of sexual arousal». *Psychological Science* 15, 2004, 736–744.

¹¹⁷ Canli, T., Gabrieli, J.D.E. «Imaging gender differences in sexual arousal». *Nature Neuroscience* 7, 2004, 325–332. Resultados confirmados midiendo la excitación con el parámetro de dilatación de la pupila. Hamann, S., *op. cit.* 100.

¹¹⁸ Cfr. además de las citas citadas anterior mente: Safron, A., Barch, B., Bailey, J.M., Gitelman, D.R., Parrish, T.B., *et al.*

sexual orientation of the individual does not generate the activation of the hypothalamus characteristic of sexual arousal neither in heterosexual men nor in homosexuals.

Erotic visual stimuli, very strong in men, are associated with the activation of the brain that processes the emotions and feelings before a sensorial stimulus, seen in this case¹¹⁹.

Heterosexual man arouses before the visualization of a scene of a couple of different sex, in a similar form, the homosexual male does before that of a male couple.

However, the cerebral strategy is not the same and areas are activated in a differential form and with a different intensity. In homosexual males it is not activated with the same intensity than in heterosexuals the right anterior cingulate cortex, that participates in the processing of visceral responses, the left insular region that participates in the recognition of the somatosensory process and the right caudate nucleus that participates in the motor control of male sexual arousal.

Both groups of males showed activation of the orbito-frontal cortex, amygdala, and hippocampus that process emotions as being positive and negative. This is, when the visual stimuli is of the same sign as their orientation of the stimulation pattern equally produces the desire but the processing of the response is not the same.

On the other hand, ante videos of the opposite orientation, showed a strong bilateral activation of the frontal inferior, more pronounced than when the stimuli corresponds with its orientation. This finding, according to the authors, can at least in part be associated with the visceral activity, as well as the adverse emotional stimuli as disgust and frightfulness. Moreover, heterosexuals show more activation of the right amygdala that processes negative emotions.

Given that stimuli of different character to one's own orientation is perceived with great emotional burden, and lead to a greater autonomic general response, more than a specific response for sexual arousal, that strong activation of the insular region is more probably to be related with diverse emotional processes, in part aversive, instead of sexual emotions per se.

Alternatively, said in another manner, the signs that the insula gives to the amygdala to evaluate emotions “according” to the function of the stimuli in the corporality, are distorted.

«Neural correlates of sexual arousal in homosexual and heterosexual men». *Behavioral neuroscience* 121, 2007, 237–248. Stoleru, S., Gregoire, M.C., Gerard, D., Decety, J., Lafarge, E., Cinotti, L., Lavenne, F., Le Bars, D., Vernet-Maury, E., Rada, H., et al. «Neuroanatomical correlates of visually evoked sexual arousal in human males». *Archives of sexual behavior* 28, 1999, 1–21. Hu, S.H., Wei, N., Wang, Q.D., et al. «Patterns of brain activation during visually evoked sexual arousal differ between homosexual and heterosexual men». *American Journal of Neuroradiology* 29, 2008, 1890–1896. Paul, T., Schiffer, B., Zwarg, T., et al. «Brain response to visual sexual stimuli in heterosexual and homosexual males». *Human Brain Mapping* 29, 2008, 726–735. Karama, S., Lecours, A.R., Leroux, J.M., Bourgouin, P., Beaudoin, G., Joubert, S., et al. «Areas of brain activation in males and females during viewing of erotic film excerpts». *Human Brain Mapping* 16, 2002, 1–13. Ponseti, J., Granert, O., Jansen, O., Wolff, S., Mehdorn, H., Bosinski, H., et al. «Assessment of sexual orientation using the hemodynamic brain response to visual sexual stimuli». *Journal of Sexual Medicine* 6, 2009, 1628–1634.

¹¹⁹ Giro prefrontal medio, lóbulo bilateral temporal, y giro central posterior, tálamo, ínsula, vermis, precúneo izquierdo, corteza occipital, parietal y cerebelo.

In this manner, the brain amygdale translates the visual perception to homosexual stimuli of attraction and reward, and processes the arousal far from the consummation to which reproduction is linked. On the contrary, heterosexual stimuli, aimed at procreation, are interpreted by the amygdale as rejection. Sexual experiences reinforce the evaluation.

In summary, the neurofunctional correlate of sexual arousal is uniform and different in men and in women, independently of sexual orientation. However, the paths are different, or strategies by which heterosexual and homosexual males process the erotic visual stimuli thereof, or in the opposite sense, towards their own sexual orientation.

6.2 Response to olfactory sexual stimuli

In most mammals odor plays a fundamental role in sexual instinct. The pheromones, chemical substances segregated by the female in the fertile period, affect the neuroendocrine brain and reproductive behavior. The neuronal network/red that processes these odors presents dimorphism¹²⁰.

In rodents dimorphism exists in the vomeronasal organ, the first neuron in a sensorial red that processes the odors related with reproduction. The information reaches the pre-optic region of the hypothalamus, where the sexually dimorphic nucleus of the pre-optic area that directs the response. In humans, the sense of smell does not have the potency, or the capacity to discriminate odors that he has of the other mammals. Humans lack the accessory olfactory bulb and the vomeronasal organ is not functional.

In general, the olfactory system before diverse smells activates some areas more in women than in males.

Some substances derived from sexual hormones act as sexual chemical sensors, when they participate in the activation of the associated centers of sexual conduct in a dimorphic matter¹²¹. In women when they smell derived compounds of androgens in high concentrations, in the hypothalamus the areas of the feminine sexual brain are activated. To the contrary, in males the masculine areas of the hypothalamus are activated when they smell estrogen type substances. The activation of the hypothalamus is therefore, also, sex-dependent. Female neuronal circuits are more sensible in the pre-ovulation period; thus, they can detect the almost imperceptible odor of androgens in the man's body odor¹²². A correlation is thereby established between the heterosexual sexual olfactory stimulus and its aim of facilitating reproduction at the start of the woman's fertile period.

The odor of derived compounds of androgens also activates the hypothalamus of homosexual males, but does not produce activation in the hypothalamus of heterosexual

¹²⁰ Guillamón, A, Segovia, S. «El sexo del cerebro». *Mente y Cerebro* 25, 2007, 68-77. Savic, I.«Processing of odorous signals in humans». *Brain Research Bulletin* 54, 2001, 307-312.

¹²¹ Savic, I, Berglund, H., Gulyas, B. Roland P. «Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans». *Neuron* 31, 2001, 661-668. Savic, I., Berglund, H. «Androstenol –a steroid derived odor- activates the hypothalamus in women». *PLoS ONE* 5(2), 2010, e8651.

¹²² Graham, C.A., Janssen, E., Sanders, S.A. «Effects of fragrance on female sexual arousal and mood across the menstrual cycle». *Psychophysiology* 37, 2000, 76-84. Grammer, K. «Androstadienone a male pheromone?» *Ethology and Sociobiology* 14, 1993, 201-207.

males. Homosexual females also react in an atypical manner¹²³. It is repeated again what is observed in relationship to erotic visual stimuli: the pleasurable response in homosexuality is disconnected from the stimulus function.

Odors in general are intensely related with emotions and memory. Thus, sensibility to this type of sexual stimulus by substances from gonadal origin have more to do with lifestyles that with an innate predisposition.

6.3 Face Perception

Face perception is modulated by sexual preference, by which the emotion that it arouses can be used as a parameter of sexual orientation. Before a woman's face the thalamus is activated with much more strength and the medial prefrontal cortex of heterosexual males and homosexual females, to both sexes while in homosexual males and heterosexual females these structures reacted with a greater force to the face of a person¹²⁴.

6.4 Bisexual people

The studies that use pupil dilation as a measurement of bisexual arousal have permitted in knowing in what bisexuality differs in males and in females.

Masculine bisexuality is not spontaneous nor of the same type in all males. Some have a bisexual arousal pattern to erotic visual stimulus, with less arousal than homosexual males or heterosexuals¹²⁵. Previously it had been described¹²⁶ that the masculine pattern is not bisexual possibly because identification as a bisexual is because of different reasons of having a strong sexual response to both sexes¹²⁷.

Very few men are really attracted to both sexes¹²⁸. The majority of males identify themselves as bisexuals, although they are only attracted to one of the sexes because of their personal lifestyle has opened up to a variety of sexual experiences which includes the relationship with their non preferred sex.

Differently from most men, many women show sexual arousal as important to both sexes. However, bisexual women do not have a bisexual response pattern. Homosexual women

¹²³ Savic, I., Berglund, H., Lindström, P. «Brain response to putative pheromones in homosexual men». *Proceedings of the National Academy of Sciences of the United States of America* 102, 2005, 7356–7361. Berglund, H., Lindström, P., Savic, I. «Brain response to putative pheromones in lesbian women». *Proceedings of the National Academy of Sciences of the United States of America* 103, 2006, 8269–8274. Ponseti, J., et al. «Homosexual women have less grey matter in perirhinal cortex than heterosexual women». *PLoS ONE* 2, 2007, e762

¹²⁴ Kranz, F., Ishai, A. «Face perception is modulated by sexual preference». *Current Biology* 16, 2006, 63–68.

¹²⁵ Rosenthal, A.M., Sylva, D., Safron, A., Bailey, J.M. «Sexual arousal patterns of bisexual men revisited». *Biological Psychology* 8, 2011, 112–115.

¹²⁶ Rieger, G., Chivers, M.L., Bailey, J.M. «Sexual arousal patterns of bisexual men». *Psychological Science* 16, 2005, 579–584.

¹²⁷ Rieger, G., op. cit. 125. Rosenthal, A.M., Sylva, D., Safron, A., Bailey, J.M. «Sexual arousal patterns of bisexual men revisited». *Biological Psychology* 8, 2011, 112–115.

¹²⁸ Savin-Williams, R.C., Joyner, K., Rieger, G. «Prevalence and stability of self reported sexual orientation identity during young adulthood». *Archives of Sexual Behavior* 41, 2012, 103–110. Laumann, E.O., Gagnon, J.H., Michael, R.T., Michaels, S. *The social organization of sexuality: Sexual practices in the United States*. University of Chicago Press, Chicago, IL, 1994.

have more typical responses than do males: they show more sexual arousal to feminine stimuli and less than heterosexual women to masculine stimuli. By average, they are more masculine in their facial traits and even in their interests and personality¹²⁹.

6.5 Consolidation of sexual orientation

Differences in sexual orientation and male and female behavior is not restricted to western cultures but that they also occur in different cultures¹³⁰. In all cultures sexual experiences as those that are not sexual, in the plastic threshold of the childhood and the adolescent brain are crucial for the conformation of sexual orientation.

As we have pointed out, prospective studies suggest that the differences in masculinity and femininity appear in infancy and before the development of an adult sexual orientation identity. The correlative development of feminine/masculine patterns and of sexual orientation is innate and includes prenatal gonadal influences and genetic influences¹³¹. Since stimulation patterns and sexual response are different, social environment influences in a different form in males and females¹³². In contrast with men, female sexual attraction patterns are less affected by the mate. They are much more affected by the cultural and social variables and by conditions¹³³. These variables include the couple's ties, the history of attachment, upbringing, experiences, attitudes, religious beliefs, and culture¹³⁴. Now, however, one's own experience supposes the strongest consolidation factor. The mark of the brain that poses the chemical modification of the DNA regions that regulate the expression of the hormone receptors, epigenetic change, is a critical component of the mechanism by which the early life experiences influence the brain.

7. Sexual Affection

The technique of functional magnetic resonance that detects emotions has allowed to establish the neural correlates that are implicated in that affection directed towards only one person, exclusive, intense and in a certain measure involuntary, known as romantic love. This is done by just observing the brain activity of subjects that were deeply in love while they saw photos of their beloved, in comparison with the activity produced by seeing

¹²⁹ Freeman, J.B., Johnson, K.L., Ambady, N., Rule, N.O. «Sexual Orientation Perception Involves Gendered Facial Cues». *Personality and Social Psychology Bulletin* 36, 2010, 1318–1331. Lippa, R.A. «Sexual Orientation and Personality». *Annual Review of Sex Research* 16, 2005, 119–153. Rieger, G., Linsenmeier, J.A.W., Gygax, L., Garcia, S.C., Bailey, J.M. «Dissecting “gaydar”: Accuracy and the role of masculinity-femininity». *Archives of Sexual Behavior* 39, 2010, 124–140.

¹³⁰ Lippa, R.A. «Sex differences and sexual orientation differences in personality: Findings from the BBC Internet survey». *Archives of Sexual Behavior* 37, 2008, 173–187.

¹³¹ Hines, M. «Gender Development and the Human Brain». *Annual Review of Neuroscience* 34, 2011, 69–88. Bailey, J.M., Dunne, M.P., Martin, N.G. «Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample». *Journal of Personality and Social Psychology* 78, 2000, 524–536.

¹³² Burri, A., Cherkas, L., Spector, T., Rahman, Q. «Genetic and environmental influences on female sexual orientation, childhood gender typicality and adult gender identity». *PLoS One* 6 (2), 2011, e21982.

¹³³ Baumeister, R.F. «Gender differences in erotic plasticity: The female sex drive as socially flexible and responsive». *Psychological Bulletin* 26, 2000, 347–374. Diamond, L.M. «Sexual fluidity: Understanding women's love and desire» Harvard University Press, Cambridge, MA, 2008.

¹³⁴ Peplau, L.A. «Rethinking women's sexual orientation: An interdisciplinary, relationship-focused approach». *Personal Relationships* 8, 2001, 1–19. Peplau, L.A. «Human sexuality: How do men and women differ?» *Current Directions in Psychological Science* 12, 2003, 37–40.

images of their friends of the same age, sex, and length of friendship as their couples¹³⁵.

It is a complex affection involves the erotic, the emotional, the cognitive, and the components of behavior. The similitude in certain aspects with a mother's love for her child¹³⁶ has helped reveal the characteristic emotions of falling-in-love. The common activated areas in both types of affective relationships form part of the circuits of awards linked to dopamine, "the happiness hormone" (the hippocampus and parts of the striatum and the accumbens nucleus) and likewise the anterior cingulate cortex, that recognizes feelings, something no doubt essential for the love relationship and the medial insular cortex. The lobe that integrates the visual sensorial information in the world of feelings, shows more activity when more attractive the countenances presented results.

To stay in love requires the brain circuits of personal relationship and the emotional memory. When this process is developed less stimulus of oxytocin and dopamine are needed to maintain the emotional bond; in this sense the initial falling-in-love, like maternal love, has somewhat of addiction; the longing for the enraptured feeling of being together can lead to a certain mutual dependence for the other. The exhibitions of affection of the couple seal the bond and trigger the brain circuits of the confidence associated with the secretion of oxytocin, with more intensity in women.

The behavior of sexual relationship is controlled by neurohormones, that increase the levels of dopamine and that differ in males and females. The masculine brain employs the vasopressin for social and familiar relationship, while the feminine brain primarily uses oxytocin¹³⁷. The receptors are widely distributed in the brain stem.

In the female brain in love as in the maternal brain but not in the masculine, the ventral region of the anterior cingulate cortex is activated. Possibly the acknowledgement of the feelings of love of this area collaborates with the silencing of the amygdale of the right side in such a way that it can quench the activity of these regions, that precisely are active in depressed states or of sadness, especially in women. This area connects with all the cerebral regions implicated in the processing of other types of emotions, like social exclusion¹³⁸ or interest to know the positive intention of interpersonal relationships. They are zones that constitute a profile of areas invariably activated with the capacity of detecting emotions and one's intentions and those of other persons. To see the face of the beloved deactivates the frontal cortex and the amygdale by which judgment becomes less severe and curiosity is discontinued and the fear that usually appears when one studies the countenances in the

¹³⁵ Bartels, A., Zeki, S. «The neural basis of romantic love». *Neuro Report* 11, 2000, 3829-3834. Zeki, S. «The neurobiology of love». *FEBS Letters* 581, 2007, 2575-2579. Aron, A., Fisher, H., Mashek, D.J., Strong, G., Li, H., et al. «Reward, motivation, and emotion systems associated with early-stage intense romantic love». *Journal of Neurophysiology* 94, 2005, 327-337.

¹³⁶ Bartels, A., Zeki, S. "The neural correlates of maternal and romantic love". *Neuro-image* 21, 2004, 1155-1166.

¹³⁷ Insel, T.R., Young, L.J. «The neurobiology of attachment». *Nature Review of Neuroscience* 2, 2001, 129-136. Loup, F., Tribollet, E., Dubois-Dauphin, M., Dreifuss, J.J. «Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study». *Brain Research* 555, 1991, 220-232

¹³⁸ Gallagher, H.L., Frith, C.D. «Functional imaging of 'theory of mind'». *Trends in cognitive science* 7, 2003, 77-83. Eisenberger, N.I., Lieberman, M.D., Williams, K.D. «Does rejection hurt? An fMRI study of social exclusion». *Science* 302, 2003, 290-292. Frith, C.D., Frith, U. «Interacting minds. A biological basis». *Science* 286, 1999, 1692-1695. Brunet, E., Sarfati, Y., Hardy-Bayle, M.C., Decety, J. «A PET investigation of the attribution of intentions with a nonverbal task». *Neuro-Image* 11, 2000, 157-166.

search for disconcerting signs. This is, the studies of neuroimagery reveal the pleasurable stimulus by the activation of the cognitive-affective system areas of reward as well as the silencing of the implicated areas of negative judgment¹³⁹.

Unlike maternal love, in falling-in-love specific areas of the hypothalamus implicated in sexuality are activated and reflects the component of erotic impulse inherent in this feeling¹⁴⁰.

7.1 Romantic love and sexual orientation

It has been described by means of the same technique of functional magnetic resonance¹⁴¹, the neural correlates of the pleasurable emotion produced by sight of the couple's face, in heterosexual males and females and in homosexuals. The study was directed towards analyzing the feeling of love in itself, that as a human feeling- with the characteristic of exclusivity towards only one person the desire of uniting between themselves and dissolving all distance, that the affection of friendship lacks-sustains itself on the same brain processes.

Differences in the activation and deactivation patterns between the groups were not found, although the sample of this study presented too many variables to show any difference in the activation or deactivation intensity if there were. It was not uniform neither respecting the time of relationship¹⁴², nor the follicular phase where women found themselves in¹⁴³, both variables that influence the response. Authors affirm that differences in the responses among those that pertain to one or the other sexual orientation would have to be found in the sexual counterpart of love, that certainly exist.

The affection crush between persons of the same sex differs from the mere affection of friendship, or of maternal affection and resembles that of a love affair between persons of different sex, as far as the impulse of an excluding union of third parties and that involves sexual practices. In this regard, the desire can be understood of some to equate both types of relationships. It is an approximation up to the point that it is considered as a fruit –“child” of a homosexual relationship between two women or two men, the one generated by in vitro fertilization with one of the couple's gamete and a third of a different sex.

Homosexual practices, obviously cannot produce a synchronized response, asymmetric and complementary that defines heterosexual consummation to which the transmission of life are bound. Neuro-sciences with the analysis of the structures and the functional dynamics

¹³⁹ Zeki, S *op. cit.* 134. Bartels, A., *op. cit.* 135

¹⁴⁰ Arnov, B.A., Desmond, J.E., Banner, L.L., Glover, G.H., Solomon, A., Polan, M.L., Lue, T.F., Atlas, S.W. «Brain activation and sexual arousal in healthy, heterosexual males». *Brain* 125 (Pt 5), 2002, 1014–1023.

¹⁴¹ Zeki, S., Romaya, J.P. «The Brain Reaction to Viewing Faces of Opposite- and Same-Sex Romantic Partners». *PLoS ONE* 5(12), 2010, e15802.

¹⁴² Kim, W., Kim, S., Jeong, J., Lee, K.U., Ahn, K.J., *et al.* «Temporal changes in functional magnetic resonance imaging activation of hetero- sexual couples for visual stimuli of loved partners». *Psychiatry Investigation* 6, 2009, 19–25.

¹⁴³ Rupp, H.A., James, T.W., Ketterson, E.D., Sengelaub, D.R., Janssen, E., *et al.* «Neural Activation in Women in Response to Masculinized Male Faces: Mediation by Hormones and Psychosexual Factors». *Evolution and human behavior* 30, 2009, 1–10.

of the brain distinguish between the similitude of sexed affection of people – whatever their sexual orientation is- with its components of exclusivity and eroticism, and the difference in the nature of heterosexual and homosexual practice, not only in the physical sense, which is obvious, but also in the cerebral. Revealing a relationship between homosexual orientation and neurobiological entities not associated with procreation highlight the impossibility of equating both types of relationships.

The taking of legal, social -especially educational- decisions in these profound aspects of human life should take into consideration the conclusions that emerge in the progress of the comprehension of the dynamic brain of people with one or another sexual orientation.

On the one hand, the equalization, that we have just referred to, can have consequences that go beyond than the couple: the affectation of the brain dynamism of the “children” of two mothers or two fathers. On the other, the dysfunction between a stimulus and its biological sense can be lived as suffering or limitation. Thus, you cannot discriminate whom voluntarily, freely needs, and looks for help to readjust the neuropsychological process.