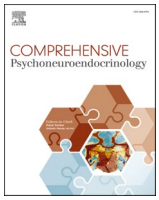
Comprehensive Psychoneuroendocrinology 16 (2023) 100198

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology



A long and winding road: My personal journey to oxytocin with no return

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ARTICLE INFO

Keywords:
Personal history
Biological psychiatry
Serotonin
Love
Oxytocin

ABSTRACT

The present paper is the personal narration of the author reviewing her scientific pathways that led her toward the study of oxytocin. My work began with a pioneering study showing a decreased number of the serotonin transporter proteins in romantic lovers. This unexpected finding promoted my interest in the neurobiology of human emotions and feelings, and significantly shifted my research focus from diseases to physiological states that underlie "love." During this time increasing experimental data broadened the spectrum of activities of oxytocin from female functions, such as parturition and lactation, to modulation of the stress and immune system. The literature also began to reveal an important role for oxytocin in a sense of safety and wellbeing, processes that are critical to both love and survival. I suggest here that future studies should disentangle different emerging questions regarding the exact role of oxytocin within human nature, as well as its possible therapeutic applications in different physiological conditions and pathological states. Understanding these, in turn, holds the potential to improve the lives of both individuals and societies.

1. The antecedents: walking and learning in the shadow of giants

I was an adult before I realized that not everyone lived near Florence or Rome or grew up in a place that inspired the Renaissance. Pisa, where I was educated, of course is known to most people for its iconic "leaning tower." However, Pisa also was the birthplace of scientists whose work helped to create the modern world. Galileo, often considered the founder of the modern scientific method came from Pisa. Fibonacci (aka Leonardo of Pisa), considered the greatest Western mathematician of the Middle Ages, lived in this area in the 12th century. The University of Pisa was formally established in 1343 and was biologically oriented from its foundation.

However, when I enrolled in medical school at the University of Pisa (Italy), I was only 18 years old. I had no idea of what kind of doctor I would like to become. I was simply interested in the human being as a whole and not specializing in the study of any single function or organ. However, as soon as I passed my examinations in Anatomy and Physiology, I realized that I was fascinated by the human brain and would find research in the fields intimately linked to the brain most fulfilling. I was encouraged to pursue my activities in psychiatry by Professor Giovanni Battista Cassano, a recently-appointed full professor of Psychiatry at Pisa University, who suggested that I prepare my graduation thesis in his department. I did and graduated in Medicine in July 1981.

1.1. The 1980s

The 1980s were an exciting period for Psychiatry and Neuroscience. At that time, the prescription of psychotropic drugs was becoming more focused, as a result of increasingly detailed diagnostic criteria and increasing contributions of biological research. Neuroscience was evolving rapidly and neuroscientific methods were becoming easier to use and, consequently, more generally available and affordable [1]. These advances began to have a real impact upon clinical research and a true link was finally being established between laboratory data and clinical practice [2]. Also, new and more targeted drugs, namely selective serotonin reuptake inhibitors (SSRIs), were being developed; these not only resulted in a radical change in the treatment of depression, but they also permitted the treatment of certain other categories of patients, such as those affected by obsessive-compulsive disorder (OCD) and related disorders that had long been considered unresponsive to psychotropic compounds [3,4]. Generally speaking there was a widespread feeling of enthusiasm; my generation of physicians felt confident that further light would soon be shed on the mysteries of the brain and neuropsychiatric conditions, now that it seemed evident that "brain = mind".

As I prepared my final thesis, I became increasingly fascinated by the emerging field of Biological Psychiatry and wanted to continue the tradition of my Department. In 1983, part of my medical residency was

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https://doi.org/10.1016/j.cpnec.2023.100198
Received 27 July 2023; Accepted 31 July 2023
Available online 4 August 2023

carried out in Psychiatry at the University of Oslo (Norway). There I had the good fortune to spend time in the laboratory of Professor Elling Kvamme. Professor Kvamme was a distinguished scientist, conducting neurochemical studies on glutaminase. This allowed me to become familiar with the basic methods employed in clinical neurochemistry. Although the experience in Norway was great, I had felt some degree of discomfort in dealing with the lab activity only. I missed contact with patients.

Therefore, when I returned to Pisa, I started working in both clinical wards and the Department's chemistry laboratory. That laboratory had been created some 20 years earlier by Professor Cassano. It was a really exciting period for me. Although I was very young, I became the person in charge of selecting scientific directions that would be pursued by our group. After a series of intensive brainstorming sessions, we decided to focus on two main research projects, involving (a) the platelet serotonin transporter and (b) the putative endocoids acting on central benzodiazepine receptors. Both targets allowed the possibility of clinical studies involving samples from psychiatric patients.

The first studies were carried out on the serotonin transporter (SERT) in depressed patients and constituted the subject of my "Specialty Thesis." These also became my first relevant international publications [5–7]. After specializing in psychiatry, I felt the need to broaden my knowledge and also technical ability and therefore began another residency in Clinical Biochemistry, training that I completed in 1990.

During this period, the activity of our laboratory was attracting an ever-increasing number of medical and biological students. Our program became substantially larger and new working arrangements were possible within other Departments throughout the University of Pisa. This provided different expertise and methods and I had the opportunity to collaborate with and explore other domains, including Biochemistry and Pharmacology in the Faculties of Pharmacology, Immunology, and Neurology, as well as Pathology in the Faculty of Medicine, and Cell Biology in the Faculty of Science and the Department of Chemistry. The link with the Department of Biochemistry became so productive that after a few years we were amalgamated into a single, much larger, interfaculty department called "Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie".

1.2. The fantastic nineties of the past century

In September of 1990, I was awarded a CINP young investigator prize in Kyoto (Japan) where I met many foreign colleagues and began collaborations with different centers, such as the Mount Sinai Medical School in New York City and the Department of Psychiatry, at the University of Georgia. For a decade for one month each year I traveled to the United States to carry out different projects.

Collaborations with different institutes abroad enabled me to enlarge my focus and areas of interest and the research projects became more varied. I began to perform pre-clinical studies, such as those in rat and calf brains, or on human brain postmortem tissues. In those models we characterized the SERT and different serotonin receptor subtypes, using *in situ* hybridization. Subsequently, we compared serotonin receptors in postmortum brain samples from patients with different psychiatric conditions, which had kindly been supplied by the NAMI Research Institute from Washington DC [[8–16]).

The nineties of the past century represent a real turning point in my professional and personal life. Since the 90's, OCD and related disorders have attracted increasing interest throughout the world and it also became one of my main interests, and I began to use available peripheral biomarkers to understand the biology of OCD. In some of my studies, our group, and others, demonstrated that OCD patients may show a reduction in the number of serotonin transporter platelets (SERT), and that these were proportional to the severity of the obsessive-compulsive symptoms involved. Furthermore these measures can returns to normal levels after specific pharmacological treatments [17–20]. However, it was difficult to recruit drug-naïve patients for a reliable assessment of the SERT. During this time, I was searching for a normal "physiological" model resembling the obsessions and/or compulsions we saw in OCD. As widely reported in the psychological and psychiatric literature, the prevalent ideation of the early phase of romantic love is very similar to a pathological obsession.

One morning I had a sort of sudden "inspiration" to study the SERT in romantic lovers. It took some months to recruit the sample with the very stringent criteria I adopted, but it gradually was possible and I had my first results. When my coworkers and I assess biomarkers, this process is conducted under totally experimentally blind conditions; that is to say, there is no possibility to identify the subjects or their clinical pathology. When my colleagues showed me the results on romantic lovers the general comments was "these are very crazy patients." I also did not trust the results and we repeated the experiments; but the results did not change. It was 1994, and I wrote the paper with Professor Hagop S. Akiskal, one of my tutors who had become a good friend. In general once I am confident of the data I usually immediately submit a paper to a journal. This time I did not do that. Indeed, I felt that this study could change my life and that I was not ready to cope with it. However, after some years I sent that paper on reduced number of the SERT in romantic lovers to *Psychological Medicine*. It was quickly published in 1999, with the editor-in-chief commending it in a hand-written accompanying letter [21].

What I did expect actually happened. For the first time in my experience, I saw clear biochemical evidence that a widely recognized emotion or feeling might have a biological substrate [21]. The results of my study on romantic love became widely discussed, even amongst the general public. Media from around the world immediately reported that a scientist had unveiled the "biological roots of love," while others claimed that I had destroyed the poetry of love (incidentally, for this reason I was awarded the IgNobel prize for chemistry!). In the years that followed I did interviews and participated in TV programs from different countries. I adapted my scientific knowledge and language to explain to nonscientists what we had discovered. It was very rewarding for me to learn how to become understandable and to share scientific data, something that might not have happened if I had not begun to study "love."

1.3. From the dawn of the third millennia to nowadays

I soon became aware that these novel findings were opening new perspectives, both scientifically and personally. I have been always considered it a privilege to have the possibility to do research in total freedom and to select which deepest part of myself to study. This freedom allowed me to shift part of my research focus from pathological conditions to normal states, while becoming increasingly aware that the border between the two is vague and influenced by many factors. I realized that people worldwide are so interested in love because this is the most extraordinary and strong experience of our nature. At the same time disruptions in love and relationships can precipitate psychopathological conditions, from anxiety to psychosis, especially amongst those with no partner, with unrequited love or after a relationship breaks up - especially when there is a sense of abandonment. Therefore, I started to pay more attention to the emotional experiences of my patients, and to transfer "cold" neuroscientific data to the bedside. From the personal point of view, I knew that I was changing and that I was profoundly affected by this kind of research; what I was doing was rewarding while touching me deeply.

1.4. The neurobiology of love

I gradually became aware that this typically feeling, what humans call "love," is the results of different stages, each managed by well-conserved (from an evolutionary point of view) and well-integrated neural substrates [22–24]. While examining the shared features in the ideation of romantic lovers and the obsessions of OCD patients, I realized

that along its various stages love must be regulated by different systems and neurotransmitters. The neurobiology of neuropsychiatric disorders, as well as emotions and feelings could not rely simply on one or a few neurotransmitters [25]. Rather, love is complex and multifaceted, and rooted in ancient brain structures. It emerges as a consequence of the dynamic interplay of different factors, such as genetics, epigenetics and environmental factors.

The earliest stage, generally called romantic love, helps us deal with the fear and anxiety associated with strangers. This requires changes in limbic brain structures and major neurotransmitters including increased monoamine levels and decreased serotonin concentrations [21,24]. The temporary state of "madness" experienced by people in the phase of romantic love may have an evolutionary purpose, as it pushes the individual to become more impulsive, to overcome fear and neophobia, and to willingly accept being close to others. Love can be considered, therefore, "a fear without fear", since it involves the same systems that regulate anxiety, fear and stress responses [26]. Overcoming fear is a universal feature of love - seen all over the world. That is to say, it allows the individual to get out of states of fear and move toward a perception of safety and eventually social support [27]. This realization was a great turning point. I felt insignificant in the face of the mysterious mechanisms of love and the magnificence of nature and the deep biology which allows these feelings. It was a great challenge to begin to explore the deeper neurobiology of love.

I had fallen in love with romantic love. At this point, the neuroscientist in me began to look for molecules that might be more specific to love. It was here that oxytocin would become my next focus. I had my first personal encounter with oxytocin while listening to a seminar given by Professor Jaak Panksepp [28]. This was during a one-month sabbatical at the National Institute of Mental Health in Bethesda in 1991. At the same time I also met Thomas Insel. Dr. Insel shared by clinical interests in OCD and later on in attachment [29,30], so meeting him also inspired me and helped my thoughts to crystalize concerning the parallels between OCD and love. Dr. Leckman was another colleague that I met at different meetings who also underlined the similarities between OCD and paternal or romantic love [31].

Around 1990, I had begun to collect the available literature on the biology of love. In that time period it began to be apparent that oxytocin was not just a female reproductive hormone - a mistaken notion that had possibly delayed it being taken seriously. It is also useful to note here that, in those days before the internet, perhaps the most difficult problem for many international scientists, was gaining access to this kind of information, often written in English and only found in good libraries. In 1998 a special issue of *Psychoneuroendocrinology* entitled "Is there a neurobiology of love" became a sort of bible for me [32]. In that volume I recall reading papers by Sue Carter and Stephen Porges, described the biology of love. I had also studied the 1990 book from Paul MacLean book called "The Triune Brain" [33]. Together, all these various contributions demonstrated how motivated states, such as love, spring from evolving brain structures.

1.5. Oxytocin

Oxytocin is primarily produced in the hypothalamus, being released in the early stages when the attraction phase starts. Oxytocin appears to "transform" the "anxiety/fear" reactions into a sense of wellbeing, reward and joy [34]. This is possible through the reduction of reactivity in the stress systems [35,36], and the activation of the reward processing, regulated by the neurotransmitter dopamine [37]. At the same time, oxytocin is released in the blood stream and conveys information to peripheral organs. Oxytocin is also produced in peripheral tissues, and can return to the brain [38], creating loops linking brain mechanisms to the periphery.

One of the most important targets for oxytocin is the vagal system. According to the polyvagal theory, first articulated by Porges in the 1990s [39–42], the activity of oxytocin on the brainstem nuclei that regulated the vagus would help to explain the different emotions and bodily changes experienced during social bonding and love. One of our studies in healthy subjects actually confirmed the relationship between anxiety during romantic attachment and oxytocin [43]. Research carried out with functional magnetic resonance imaging showed activation in brain areas, believed to be rich in OT receptors when an individuals look at pictures of the partners [44,45]. Subsequent authors confirmed these findings, while highlighting how love can be a strong motivational state, creating activity in the neuronal circuitry of reward and pleasure [46] and showing that long-term love activates the attachment system [47].

It is now evident that oxytocin is an extraordinary peptide and exerts a multiplicity of activities. Oxytocin acts as a potent modulator of the immune system and of anxiety and fear response, mainly with anxiolytic effects, even during development [36,43,48–51], and it plays a prominent role in homeostatic cellular processes [52]. Many of its anti-inflammatory actions appear to be, at least in part, exerted through the attenuation of inflammatory processes mediated by microglia and macrophages [53–55]. Given its particular modulatory functions, oxytocin may link social behaviours and experiences together with the capacity to physically and emotionally heal in the face of stress or trauma, perhaps with a sexually dimorphic effect. For example, in healthy subjects, we recently found that women showed higher levels of oxytocin than men [56]. Is this fortuitous? My personal opinion is that it is not if we reflect on the notion that the most extreme, generous and altruistic forms of love are feminine: just recall the tragedy of Medea or Anne Karenina. Again, some of our data indicated that in some psychiatric disorders, specifically, OCD, post-traumatic stress disorder (PTSD) or major depressive disorder (MDD), no sex-related difference was detected, as if in these pathological conditions women might lose some of their protection (or men might began to secrete extra oxytocin to cope?) [57–60]. Overall, in that study oxytocin levels were higher in OCD, lower in PTSD and lowest MDD patients, when compared to healthy subjects. Naturally, other findings are necessary to draw firm conclusions on this topic, especially those on sex differences in oxytocin and vasopressin receptors [61,62], that may be relevant to the response to trauma and vulnerability to disease [63–67].

Taken together, available data shows that oxytocin acts in close intertwining with other systems and processes. Interestingly, using peripheral biomarkers we demonstrated the existence of a positive relationship between oxytocin and, my first love, serotonin [68–70], and more recently of a negative link with the brain-derived-neurotrophic factor (BDNF) (submitted).

2. Conclusions

New findings may answer some questions, and also may raise other doubts and problems and open new horizons. This is science that is (or should be) nurtured by doubts rather than by certainties. Scientists should always be ready to abandon their beliefs on the basis of emerging data. My personal scientific story is just one example. Each time you start on a new path, this may lead to unexpected harbours, and you must be flexible to accept that this process changes you.

In the past I was in love with serotonin. Subsequently I fell in love with love. Nowadays I love oxytocin. My deepest passion is for science itself. However, as a scientist I remain "polyamorous" and open to other new relationships. My long career in science taught me that scepticism is essential. My own experiences have taught me that the most extraordinary human feelings, those associated with the healing power of love, may depend (at least in part) on oxytocin. I must admit that I am increasingly fascinated by oxytocin, perhaps still seeing it through the eyes of "romantic infatuation." However, oxytocin is part of a complex, integrated system with multiple activities supporting coping with trauma, resilience, health, wellbeing and love [52,71].

What I learnt from studying love and oxytocin is that in humans the deep biology of love represents one of our most extraordinary attributes, enabling us to reach our highest self-realization, especially when we can

create safe social bonds and emotionally lose ourselves in another. Relationships are important for survival. Cooperation has been identified as an essential element of our evolution, and this should not be limited to close humans, but to all human beings. Oxytocin is not racist. The excessive selfishness and anthropocentrism of the latest decades has produced negative consequences for our environment that may endanger our survival as a species. I think it is now the time to take into consideration, not just our own needs, but also our ties with nonhuman animals and non bioptic elements permitting life on Earth. This will demand that we exercise empathy, altruism and oxytocin-based qualities, not only towards other members of our own species and generations of humans that will follow us, but also towards our planet.

Declaration of competing interest

None.

Acknowledgements

I am grateful to my family that supported my healthy growth and independence, while constantly nurturing my life with love, openness to the world, altruism and generosity, and promoting my curiosity and school career. I want to thank Prof. Giovanni Battista Cassano who always left the door of his office open and never refused to talk with me or other coworkers. He allowed me to be free in my research choices and to become what I could, while insisting in establishing international collaborations. As it is impossible to list all the scientists and colleagues who paved the way and shaped my interests, I want herein express my warmest gratitude to Sue Carter for what she discovered, and for what she is pursuing nowadays with her unique X devotion and enthusiasm I can feel in every of her activities, so that I consider a privilege to be listed amongst her friends. A special thank goes to all patients that I have been visiting and continue to seek for my help, as they represent a challenge and a source of inspiration. Again, I want to thank all the students and residents who have been working or are now collaborating with me, because everyday they X transmit me their desire for novelty and, on the same time, increase my sense of responsibility for their future. Last, but not least, I am grateful to the nature that created love to give a sense to our lives and to overcome adversities. Personally, I must confess herein that in 2001 I had to cope with the sudden death of my husband, but the study of the neurobiology of love and of oxytocin triggered my resilience and possibly saved me, while also accompanying me towards the accomplishment of a more mature, but extremely rewarding unexpected romantic relationship.

References

[1] W.M. Cowan, D.H. Harter, E.R. Kandel, The emergence of modern neuroscience: some implications for neurology and psychiatry, Annu. Rev. Neurosci. 23 (2020) 343–349, https://doi.org/10.1146/annurev.neuro.23.1.343.

[2] H.Y. Meltzer, Psychopharmacology: the Third Generation of Progress, Raven press, New York, 1987.

[3] E. Hollander, A. Kaplan, A. Allen, C. Cartwright, Pharmacotherapy for obsessive-compulsive disorder, Psychiatr, Clin. North. Am. 23 (3) (2000) 643–656, https://doi.org/10.1016/s0193-953x(05)70186-6.

[4] D. Marazziti, G. Consoli, Treatment strategies for obsessive-compulsive disorder, Exp. Op. Pharmacother 11 (3) (2010) 331–343, https://doi.org/10.1517/14656560903446948.

[5] D. Marazziti, g. Perugi, ja. Deltito, A. Lenzi, i. Maremmani, G.f. Placidi, G. B. Cassano, High-affinity [^{3}H]-imipramine binding sites: a possible state-dependent marker for major depression, Psychiatry Res. 23 (2) (1988) 229–237, https://doi.org/10.1016/0165-1781(88)90013-3.

[6] D. Marazziti, E. Macchi, A. Rotondo, G.B. Placidi, G.B. Cassano, Involvement of serotonin system in bulimia, Life Sci. 43 (25) (1988) 2123–2126, https://doi.org/10.1016/0024-3205(88)90362-1.

[7] D. Marazziti, S. Michelini, C. Martini, G. Giannaccini, A. Lucacchini, G.B. Cassano, Further investigation on Benzodiazepine Binding inhibitory activity (B.B.I.A.) in patients with major depression or panic disorder and in healthy volunteers, Neuropsychobiology 2 (1989) 11–13, https://doi.org/10.1159/000118544.

[8] D. Marazziti, L. Palego, M. Pasqualetti, S. Marracci, A. Batistini, I. Nardi, G. B. Cassano, Applications of molecular biology and expression studies to the investigation of serotonin receptor subtypes in human brain, Int. Rev. Psychiatr. 7 (1995) 99–104, https://doi.org/10.3109/09540269509022978.

[9] D. Marazziti, L. Palego, A. Rotondo, M. Pasqualetti, G. Giannaccini, A. Lucacchini, H. Ladinsky, G.B. Cassano, I. Nardi, Presence of serotonin1A (5-HT1A) receptor mRNA without binding of 3H-8-OH-DPAT in peripheral blood mononuclear cells, Life Sci. 57 (1995) 2197–2203.

[10] M. Pasqualetti, I. Nardi, H. Ladinsky, D. Marazziti, I. Nardi, G.B. Cassano, Comparative anatomical distribution of serotonin 1A, 1Da and 2A receptor mRNAs in human brain postmortem, Mol. Brain Res. 39 (1996) 223–233, https://doi.org/10.1016/0169-328x(96)00026-5.

[11] M. Pasqualetti, M. Ori, M. Castagna, D. Marazziti, G.B. Cassano, I. Nardi, Distribution and cellular localization of the serotonin type 2C receptor messenger RNA in human brain, Neuroscience 92 (2) (1996) 601–611, https://doi.org/10.1016/s0306-4522(99)00011-1.

[12] M. Pasqualetti, M Ori, I. Nardi, G.. Cassano, M. Castagna, D. Marazziti, Distribution of serotonin 5A receptors in human brain, Mol. Brain Res. 56 (1998) 1–8, https://doi.org/10.1016/s0169-328x(98)00003-5.

[13] M. Pasqualetti, M. Ori, M. Castagna, G.B. Marazziti, I. Cassano, Nardi, Distribution and cellular localization of the serotonin type2C receptor messenger RNA in human brain, Neurosciences 92 (1999) 601–611.

[14] D. Marazziti, L. Palego, A. Giromella, M.R. Mazzoni, F. Borsini, N. Mayer, A. G Naccarato, A. Lucacchini, G.B. Cassano, Region-dependent effects of of flibanserin and buspirone on adenylyl cyclase activity in the human brain, Int. J. Neuropharmacol. 5 (2002) 131–140.

[15] D. Marazziti, G. Giannaccini, L. Giromella, D. Betti, I. Pesce, A. Nardi, A. Rossi, G. B. Cassano, A. Lucacchini, [^{3}H]-ketanserin binding sites in different psychiatric disorders, Neurochem. Int. 42 (6) (2003) 511–516, https://doi.org/10.1016/s0197-0186(02)00093-1.

[16] D. Marazziti, S. Baroni, A. Pirone, G. Giannaccini, L. Betti, L. Schmid, E. Vatteroni, L. Palego, F. Borsini, F. Bordi, I. Piano, C. Gargini, M. Castagna, M. Catena-Dell'Osso, A. Lucacchini, Distribution of serotonin receptor of type 6 (5-HT$_6$) in human brain post-mortem. A pharmacology, autoradiography and immunohistochemistry study, Neurochem. Res. (5) (2012) 920–927.

[17] D. Marazziti, E. Hollander, P. Lensi, S. Ravagli, G.B. Cassano, Peripheral markers of serotonin and dopamine function in obsessive-compulsive disorder, Psychiatr. Res. 42 (1) (1993) 41–51, https://doi.org/10.1016/0165-1781(92)90037-4.

[18] D. Marazziti, A. Rossi, G. Gemignani, G. Giannaccini, C. Pfanner, A. Milanfranchi, S. Presta, A. Lucacchini, G.B. Cassano, Decreased platelet 3H-paroxetine binding in obsessive-compulsive patients, Neuropsychobiology 34 (4) (1996) 184–187, https://doi.org/10.1016/s0165-1781(99)00102-x.

[19] D. Marazziti, F. Mungai, I. Masala, S. Baroni, L. Vivarelli, F. Ambrogi, M. Catena Dell'Osso, G. Consoli, L. Massimetti, L. Dell'Osso, Normalisation of immune cell imbalance after pharmacological treatments of patients suffering from obsessive-compulsive disorder, J. Psychopharmacol. 23 (5) (2008) 567–579, https://doi.org/10.1177/0269881108089605.

[20] D. Marazziti, L. Dell'Osso, I. Masala, S. Baroni, S. Presta, G. Giannaccini, E. Di Nasso, F. Mungai, G.B. Cassano, A. Lucacchini, Decreased inhibitory activity of PKC in OCD patients after 6 months of treatment, Psychoneuroendocrinology 27 (2002) 769–776, https://doi.org/10.1016/s0924-9338(02)00697-1.

[21] D. Marazziti, H.S. Akiskal, A. Rossi, G.B. Cassano, Alteration of the platelet serotonin transporter in romantic love, Psychol. Med. 29 (3) (1999) 741–745, https://doi.org/10.1017/s0033291798007946.

[22] D. Marazziti, Neurobiology and hormonal aspects of romantic attachment, in: M. De Haan, M.N. Gunnar (Eds.), Handbook of Developmental and Social Neuroscience, Guilford Press, New York, 2009, pp. 265–280.

[23] D. Marazziti, S. Palermo, F. Mucci, The science of love: state of the art, Adv. Exp. Med. Biol. 1331 (2021) 249–254, https://doi.org/10.1007/978-3-030-74046-7.

[24] D. Marazziti, D. Canale, Hormonal changes when falling in love, Psychoneuroendocrinology 29 (7) (2004) 931–936, https://doi.org/10.1016/j.psyneuen.2003.08.006.

[25] J.E. LeDoux, Emotion circuits in the brain, Annu. Rev. Neurosci. 23 (2000) 155–184, https://doi.org/10.1146/annurev.neuro.23.1.155.

[26] D. Marazziti, Beyond emotion: love as an encounter of myth and drive, Emotion Rev 8 (2) (2015) 110–112, 10.11772F1754073915594437.

[27] S.W. Porges, Polyvagal theory: a science of safety, Front. Integr. Neurosci. 16 (2022), 87122, https://doi.org/10.3389/fnit.2022.871227. May 10.

[28] J. Panksepp, L. Biven, The Archaeology of Mind: Neuroevolutionary Origins of Human Emotion, W. W. Norton & Company, New York, 2012, 2012.

[29] T.R. Insel, H.S. Akiskal, Obsessive-compulsive disorder with psychotic features: a phenomenologic analysis, Am. J. Psychiatr. 143 (12) (1986) 1527–1533, https://doi.org/10.1176/ajp.143.12.1527.

[30] T.R. Insel, L.J. Young, The neurobiology of attachment, Nat. Rev. Neurosci. 2 (2001) 129–136, https://doi.org/10.1038/35053579.

[31] J.F. Leckman, L.C. Mayes, Preoccupations and behaviors associated with romantic and parental love. Perspectives on the origin of obsessive-compulsive disorder, Child & Adol Psychiat Clin North America 8 (1999) 635–665.

[32] Is there a neurobiology of love? proceedings of a conference. Stockholm, Sweden, August 28-31, Psychoneuroendocrinology Nov vol. 23 (1998) 749–1013, 8.

[33] D. MacLean, the Triune Brain in Evolution. Role in Paleocerebral Functions, Plenum Press, New York, 1990.

[34] M. Kosfeld, P.J. Heinrichs, U. Zak, E. Fischbacher, Oxytocin increases trust in humans, Nature 435 (2005) 673–676, https://doi.org/10.1038/nature03701.

[35] C.S. Carter, Sex, love and oxytocin: two metaphors and a molecule, Neurosci. Biobehav. Rev. 143 (2022), 104948, https://doi.org/10.1016/j.neubiorev.2022.104948.

[36] C.S. Carter, M.A. Kingsbury, Oxytocin and oxygen: the evolution of a solution to the 'stress of life', Aug 29, Phil. Trans. R. Soc. London B. Biol. Sci 377 (1858) (2022), 20210054, https://doi.org/10.1098/rstb.2021.0054. Epub 2022 Jul 11.
[37] M. Heinrichs, T. Baumgartner, C. Kirschbaum, U. Ehlert, Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress, Biol. Psychiatr. 54 (12) (2003) 1389–1398, https://doi.org/10.1016/s0006-3223(03)00465-7.
[38] H. Yamamoto, H. Higashida, Rage oxytocin transport into the brain, Commun. Biol. 3 (2020) 70–75, https://doi.org/10.1038/s42003-020-0799-2.
[39] S.W. Porges, Orienting in a defensive world: mammalian modifications of our evolutionary heritage, A polyvagal theory, Psychophysiol. 32 (4) (1995) 301–318, https://doi.org/10.1111/j.1469-8986.1995.tb01213.x.
[40] S.W. Porges, Love: An emergent property of the mammalian autonomic nervous system, Psychoneuro 23 (1998) 837–861, https://doi.org/10.1016/s0306-4530(98)00057-2.
[41] S.W. Porges, S.A. Furman, The early development of the autonomic nervous system provides a neural platform for social behavior: a polyvagal perspective, Infant Child Dev. 20 (1) (2011) 106–118, https://doi.org/10.1002/icd.688.
[42] J. Baileya, S.F. Dugarda, S.F. Smith, S.W. Porges, Appeasement replacing Stockholm syndrome as a definition of a survival strategy, Eur. J. Psychoytrauma 14 (1) (2023), 2161038, https://doi.org/10.1080/20008066.2022.2161038.
[43] D. Marazziti, B. Dell'Osso, S. Baroni, F. Mungai, M. Catena, P Rucci, F. Albanese, G. Giannaccini, L. Betti, L. Fabbrini, A. Italiani, A. Del Debbio, A. Lucacchini, L. Dell'Osso, A relationship between oxytocin and anxiety of romantic attachment, Clin. Pract. Epidemiol. Ment. Health 4 (2006) 28, https://doi.org/10.1186/1745-0179-2-28.
[44] A. Bartels, S. Zeki, The neural basis of romantic love, Neuroreport 11 (17) (2000) 3829–3834, https://doi.org/10.1097/0001756-200011270-00046.
[45] H.E. Fisher, A.D. Aron, H. Mashek, L. Li, L. Brown, Defining the brain systems of lust, romantic attraction, and attachment, Arch. Sex. Behav. 31 (5) (2002) 413–419, https://doi.org/10.1023/a:1019888024255.
[46] A. Aron, D.J. Fisher, G. Mashek, H. Strong, L.L. Li, Reward, motivation, and emotion systems associated with early-stage intense romantic love, J. Neurophysiol. 94 (2005) 327–337, https://doi.org/10.1152/jn.00838.2004.
[47] B.P. Acevedo, A. Aron, H.E. Fisher, L.L. Brown, Neural correlates of long-term intense romantic love, Soc. Cognit. Affect Neurosci. 7 (2) (2012) 145–159, https://doi.org/10.1093/scan/nsq092.
[48] M.M. McCarthy, C.H. McDonald, P.J. Brooks, P.D. Goldman, An anxiolytic action of oxytocin is enhanced by estrogen in the mouse, Physiol. Behav. 60 (1996) 1209–1215, https://doi.org/10.1016/s0031-9384(96)00212-0.
[49] K. Uvnas-Moberg, M. Petersson, Oxytocin, Ein Vermittler von Antistress, Wohlbefinden, sozialer Interaktion, Wachstum und Heilung [Oxytocin, a mediator of anti-stress, well-being, social interaction, growth and healing], Z. Psychosom. Med. Psychother. 51 (2005) 57–80, https://doi.org/10.13109/zptm.2005.51.1.57.
[50] C.S. Carter, The role of oxytocin and vasopressin in attachment, Psychodyn. Psychiatry 45 (2017) 499–517, https://doi.org/10.1521/pdps.2017.45.4.499.
[51] B.J. Ellis, A.J. Horn, C.S. Carter, M.H. van IJzendoorn, M.J. Bakermans-Kranenburg, Developmental programming of oxytocin through variation in early-life stress: four meta-analyses and a theoretical reinterpretation, Clin. Psychol. Rev. 86 (2021), https://doi.org/10.1016/j.cpr.2021.10198.
[52] C.S. Carter, E.L. Kenkel, S.R. MacLean, A.M. Wilson, J.R. Perkeybile, C.F. Yee, H. P. Ferris, S.W. Nazarloo, J.M. Porges, J.J. Davis, M.A. Connelly, Kingsbury, is oxytocin "nature's medicine"? Pharmacol Rev. Oct 72 (4) (2020) 829–861, https://doi.org/10.1124/pr.120.019398. PMID: 32912963.
[53] K. Karelina, B. Stuller, N. Jarrett, J. Zhang, G.J. Wells, A.C. Norman, De Vries, Oxytocin mediates social neuroprotection after cerebral ischemia, Stroke 42 (2011) 3606–3611, https://doi.org/10.1161/STROKEAHA.111.628008.
[54] N. Szeto, A.J. Sun-Suslow, R.I. Mendez, K.V. Wagner, P.M. McCabe, Regulation of the macrophage oxytocin receptor in response to inflammation, Am. J. Physiol. Endocrinol. Metab. 312 (2017) E183–E189, https://doi.org/10.1152/ajpendo.00346.2016.
[55] M. Mairesse, J. Zinni, R. Pansiot, C. Hassan-Abdi, M. Demene, C. Colella, A. Charriaut-Marlangue, M. Rideau Batista Novais, S. Tanter, P. Maccari, D. Gressens, N. Vaiman, Soussi-Yanicostas, O. Baud, Oxytocin receptor agonist reduces perinatal brain damage by targeting microglia, Glia 67 (2019) 345–359, https://doi.org/10.1002/glia.23546.
[56] D. Marazziti, S. Baroni, F. Mucci, A. Piccinni, I. Moroni, G. Giannaccini, C. Carmassi, G. Massimetti, L. Dell'Osso, Sex-related differences in plasma oxytocin levels in human, Mar 26, Clin. Pract. Epidemiol. Ment. Health 15 (2019) 58–63, https://doi.org/10.2174/1745017901915010058.
[57] D. Marazziti, M. Catena Dell'Osso, The role of oxytocin in neuropsychiatric disorders, Curr. Med. Chem. 15 (2008) 698–704, https://doi.org/10.2174/092986708783885291.
[58] D. Marazziti, S. Baroni, G. Giannaccini, M. Catena-Dell'Osso, A. Piccinni, G. Massimetti, L. Dell'Osso, Plasma oxytocin levels in untreated adult obsessive-compulsive disorder patients, Neuropsychobiology 72 (2015) 74–80, 2015.
[59] C. Carmassi, D. Marazziti, F. Mucci, A. Della Vecchia, F.M. Barberi, S. Baroni, G. Giannaccini, L. Palego, G. Massimetti, L. Dell'Osso, Decreased plasma oxytocin levels in patients with PTSD Jul 1, Front Psychol 12 (2021) 612338, https://doi.org/10.3389/fpsyg.2021.612338.
[60] D. Marazziti, C.S. Carter, C. Carmassi, A. Della Vecchia, F. Mucci, G. Pagni, M. G. Carbone, S. Baroni, G. Giannaccini, L. Palego, L. Dell'Osso, Sex matters: the impact of oxytocin on healthy conditions and psychiatric disorders, Dec 16, Compr Psychoneuroendocrinol 13 (2022) 100165, https://doi.org/10.1016/j.cpnec.2022.100165. PMID: 36590869; PMCID: PMC9800179..
[61] S.M. Freeman, L.J. Young, Comparative perspectives on oxytocin and vasopressin receptor research in rodents and primates: translational implications, J. Neuroendocrinol. Apr 28 (4) (2016), https://doi.org/10.1111/jne.12382.
[62] E. Andari, K.R. Rilling, Genetic and epigenetic modulation of the oxytocin receptor and implications for autism, Neuropsychopharmacology Jan 46 (1) (2021) 241–242, https://doi.org/10.1038/s41386-020-00832-3.
[63] B. BuemannK, K. Uvnäs-Moberg, Oxytocin may have a therapeutical potential against cardiovascular disease, Possible pharmaceutical and behavioral approaches, Med. Hypotheses 138 (2020), 109597.
[64] T. Li, P. Wang, S.C. Wang, Y.F. Wang, Approaches mediating oxytocin regulation of the immune system, Front. Immunol. 7 (2016) 693.
[65] G. Clodi, R. Vila, M. Geyeregger, T.M. Riedl, J. Stulnig, J. Struck, A. Luger, Luger, Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men, Am. J. Physiol. Endocrinol. Metab. 295 (3) (2008) E686–E691, https://doi.org/10.1152/ajpendo.90263.2008.
[66] H. Amini-Khoei, S. Mohammadi-Asl, M.J. Amiri, M. Hosseini, M. Momeny, M. Hassanipour, A. Rastegar, A.H. Haj-Mirzaian, H. Mirzaian, S. E. Sanjarimoghaddam, A.R. Mehr, Dehpour, Oxytocin mitigated the depressive-like behaviors of maternal separation stress through modulating mitochondrial function and neuroinflammation, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 76 (2017) 169–178, https://doi.org/10.1016/j.pnpbp.2017.02.022.
[67] B. Buemann, D. Marazziti, K. Uvnäs-Moberg, Can intravenous oxytocin infusion counteract hyperinflammation in COVID-19 infected patients? World J. Biol. Psychiatry. Jun 22 (5) (2021) 387–398, https://doi.org/10.1080/15622975.2020.1814408.
[68] D. Marazziti, What came first: dimensions or categories? Br. J. Psychiatry 178 (2001) 478–479, https://doi.org/10.1192/bjp.178.5.478-b.
[69] D. Marazziti, Understanding the role of serotonin in psychiatric diseases, F1000 Res. Feb 23 (6) (2017) 180, https://doi.org/10.12688/f1000research.10094.
[70] D. Marazziti, S. Baroni, G. Giannaccini, L. Betti, G. Massimetti, C. Carmassi, M. Catena Dell'Osso, A link between oxytocin and serotonin in humans: supporting evidence from peripheral markers, Eur. Neuropsychopharmacol 22 (8) (2012) 578–583, https://doi.org/10.1016/j.euroneuro.2011.12.010.
[71] M. Feldman, M. Monakhov, R. Pratt, P. Ebstein, Oxytocin pathway genes: evolutionary ancient system impacting on human affiliation, sociality, and psychopathology.", Biol. Psychiatr. 79 (3) (2016) 174–184, https://doi.org/10.1016/j.biopsych.2015.08.008.