Orgasm and Related Disorders Depend on Neural Inhibition Combined With Neural Excitation

Barry R. Komisaruk, PhD,[1] and Maria Cruz Rodriguez del Cerro, PhD[2]

ABSTRACT

Introduction: Prevalent models of sexual desire, arousal and orgasm postulate that they result from an excitatory process, whereas disorders of sexual desire, arousal and orgasm result from an inhibitory process based on psychosocial, pharmacological, medical, and other factors. But neuronal excitation and active neuronal inhibition normally interact at variable intensities, concurrently and continuously. We propose herein that in conjunction with neuronal excitation, neuronal inhibition enables the generation of the intense, non-aversive pleasure of orgasm. When this interaction breaks down, pathology can result, as in disorders of sexual desire, arousal, and orgasm, and in anhedonia and pain. For perspective, we review some fundamental behavioral and (neuro-) physiological functions of neuronal excitation and inhibition in normal and pathological processes.

Objectives: To review evidence that the variable balance between neuronal excitation and active neuronal inhibition at different intensities can account for orgasm and its disorders.

Methods: We selected studies from searches on PubMed, Google Scholar, Dialnet, and SciELO for terms including orgasm, neuronal development, Wallerian degeneration, prenatal stress, parental behavior, sensorimotor, neuronal excitation, neuronal inhibition, sensory deprivation, anhedonia, orgasmic disorder, hypoactive sexual desire disorder, persistent genital arousal disorder, sexual pain.

Results: We provide evidence that the intensity of neuronal inhibition dynamically covaries concurrently with the intensity of neuronal excitation. Differences in these relative intensities can facilitate the understanding of orgasm and disorders of orgasm.

Conclusion: Neuronal excitation and neuronal inhibition are normal, continuously active processes of the nervous system that are necessary for survival of neurons and the organism. The ability of genital sensory stimulation to induce concurrent neuronal inhibition enables the stimulation to attain the pleasurable, non-aversive, high intensity of excitation characteristic of orgasm. Excessive or deficient levels of neuronal inhibition relative to neuronal excitation may account for disorders of sexual desire, arousal and orgasm. **Komisaruk BR, Rodriguez del Cerro MC. Orgasm and Related Disorders Depend on Neural Inhibition Combined With Neural Excitation. Sex Med Rev 2022;10:481–492.**

Key Words: Orgasm; Excitation; Inhibition; HSDD; FOD; PGAD; Anhedonia; Pain; Prenatal stress; Analgesia

INTRODUCTION

Evidence is reviewed herein that sensory excitation can feel pleasurable in proportion to its intensity, and that concurrent inhibition can prevent intense sensory stimulation from becoming aversive or painful, thereby enabling it to increase to pleasurably high intensity. (In this manuscript, when we refer to "high intensity" in neural terms, we mean relatively high number of action potentials per unit time or relatively high level of arousal; in mechanical sensory stimulation terms, we mean relatively high applied physical force). Throughout the nervous system, while activity of most of the neurons produce activation of the neurons to which they project, an estimated 40% of neurons *inhibit* the activity of the neurons to which they project.[1] Sensory stimulation activates both excitatory and inhibitory neurons to varying intensities, evident even at the simplest reflex levels. Increasing intensity of sensory stimulation-elicited excitation induces increasing intensity of inhibitory neural activity, a process that *enables* the excitatory activity to increase in intensity without becoming aversive.[2-4] While sensory stimulation-induced activation of the endogenous analgesia-producing systems can elevate pain thresholds,[5] the very existence of "pain threshold" signifies that there is a limit to this process, such that at the point at which the pain threshold is exceeded, the excitation is perceived as aversive or painful. It is the relative intensity of

Received May 27, 2022. Accepted July 21, 2022.

[1]Department Psychology, Rutgers University, Newark, NJ, USA;

[2]Department Psychobiology, Universidad Nacional de Educación a Distancia, Madrid, Spain

https://doi.org/10.1016/j.sxmr.2022.07.001

excitation and inhibition that determines whether the perception is pleasurable, intensely pleasurable (eg, orgasmic), aversive, or painful. At innocuous intensities of tactile sensory stimulation, blockage of inhibitory interneuron neurotransmitter action within the spinal cord can render otherwise innocuous, even pleasurable, tactile stimulation painful, a clinical condition termed "allodynia."[6-9] This implies that pain can occur even at low, as well as high, perceived intensities. In the case of genital sensory stimulation, the more intense, the more pleasurable.[2] However, genital stimulation can be painful,[10] most likely depending on whether the inhibitory activity is at a level that prevents the excitatory activity from becoming aversive. Based on the basic principle in which active inhibition is inextricably and continuously linked to active excitation, we propose herein to account for the differences among the experience of orgasm, orgasmic anhedonia (eg, pleasure dissociative orgasmic disorder), orgasmic disorder, and hypoactive sexual desire disorder.

The role of neuronal excitation and neuronal inhibition in sexual function in our concept differs in a crucial way from the way in which multiple authors have utilized the concept of excitation and inhibition. The models of excitation and inhibition of those authors (eg,[11-15]) refer to the net positive or negative *overt* effects on the behavioral components of sexual response, for example, premature ejaculation or delayed ejaculation[16] or HSDD.[15] In contrast, our concept addresses the multiple different (neuro)-physiological *components* of sexual response. This is exemplified in the case in which neuronal excitation increases to the high *pleasurable* intensity of orgasm, while concurrently, neuronal inhibition increases to the high *pain-inhibiting* intensity of orgasm. Our concept recognizes the multiple (neuro)-physiological components of sexual response in which both active excitation and active inhibition occur simultaneously, controlling multiple different but interdependent, processes that form the orgasmic "symphony" of neurological, physiological, and behavioral activity. Our concept does not refute the others; it addresses a different, neuronal aspect, of sexual function.

For perspective, we review the crucial importance of neuronal excitation, generated by sensory stimulation, for survival of neurons and, by extension, development and survival of the nervous system and hence life. We review evidence of the biological necessity for neuronal excitation to keep neurons alive. This biological imperative generates behavior that actively seeks and obtains sensory stimulation, "reinforcing," hence repeating, response to beneficial stimuli and eliciting withdrawal from noxious stimuli.[17] Reinforcement, that is, repetition of performance that obtains non-aversive sensory stimulation, has evolved as "reward," which we humans interpret as "pleasure." Intense sensory excitation that is not aversive generates intense pleasure, as in orgasm.[2] The neuronal mechanism of active inhibition can prevent excitation from reaching aversive intensities. Active inhibition thus enables excitation to reach higher intensities before becoming aversive than could occur in the absence of the inhibition. An implication of this formulation is that variation in the intensities of concurrent excitation and inhibition can account for a variety of disorders of orgasm.

DEVELOPMENT AND SURVIVAL OF THE NERVOUS SYSTEM DEPENDS ON NEURONAL EXCITATION

Sensory stimulation is not only the source of our conscious awareness and adaptive interaction with the environment, it is essential to the survival of the nervous system, for neurons die if they do not receive stimulation. While the synaptic connectivity among neurons provides an infinite variety of combinations, neuronal excitation is represented by the limited capability of each neuron. Any neuron can only fire action potentials faster, slower, or not at all, thereby releasing one or more specific neurotransmitters, which excites or inhibits the firing of action potentials of the neurons with which it connects synaptically. Neuronal activity keeps post-synaptic neurons alive, as exemplified in the following studies. In the kitten, using a blindfold over one eye to produce monocular light and form deprivation, after 2-3 months there was a marked atrophy of cells in the lateral geniculate body, which is the thalamic visual relay site.[18] If in adult animals and humans, a sensory nerve pathway is severed, "Wallerian degeneration" of the nerve fibers occurs, and neurons to which the severed nerve projects, can degenerate across one or more sequential synapses.[19] In a recent report in humans, magnetic resonance imaging of the brain after surgical removal of an eye showed clear degeneration in the (post-synaptic) ipsilateral geniculate nucleus, to which the optic tract projects; the authors also reported that surgical removal of a tumor in the temporal lobe resulted in post-synaptic degeneration in the ipsilateral mamillary body of the hypothalamus to which it projects.[20] In humans, after spinal cord injury at the cervical level, peripheral motor axons below the level of the lesion exhibited severe degeneration.[21] Transection of the spinal cord at T8-10 resulted in degeneration of motor neurons at L4-5 in rats.[22] Injury to the sciatic nerve in rats resulted in post-synaptic degeneration in lumbar spinal cord neurons.[23] In the interesting case of amputation of a hand, post-synaptic Wallerian degeneration occurred that led to degeneration of the post-synaptic neurons across 2 successive synapses in the 3-neuron chain from the hand to the cortex. This resulted in degeneration of the field of the thalamocortical neurons from the hand, such that there was sprouting of adjacent thalamocortical neurons from face and shoulder to the surviving cortical neurons that previously responded to the hand. This led to the patient feeling as if his phantom hand was being stimulated when either his face or his shoulder was touched.[24] In related cases reported by these authors, amputation of a foot, which, in the sensory cortex is represented adjacent to the genitals, resulted in perception of genital stimulation-induced orgasm being perceived also in the phantom foot. This is an indication that the intense neuronal activation at orgasm can spread excitation to adjacent neurons.[24] The above studies, using different paradigms, all demonstrate that without sufficient neuronal activity input, the receptive (post-synaptic) neurons die. Thus, synaptic input resulting from neuronal action potentials is a requirement for neuronal survival and function.

BEHAVIOR AND PHYSIOLOGY ENSURE THE ACQUISITION OF SENSORY STIMULATION

The imperative to keep neurons alive through synaptic activity has likely led to the evolution of behavior patterns that actively seek and obtain sensory stimulation that reinforces approach behavior if beneficial, and withdrawal behavior if noxious.[17] Glickman and Schiff[25] conceptualized that proprioceptive activity resulting from behavioral movement *per se* is the fundamental motivation for

organisms to generate overt motor activity. It is likely that such stimulation that is beneficial to the nervous system and the individual is what we perceive as "pleasurable," hence providing an evolutionary imperative to perpetuate behavior patterns that obtain the stimulation, for example, sexual behavior and orgasm.

Compensatory (neuro-) physiological Processes that Ensure Sensory Stimulation

Earliest in our development, physical contact with mother or other caretaker provides us with sensory stimulation—loving, caressing touch, sounds, odors.[26] Psychiatrists have emphasized the role of physical[27] and even symbolic social[28] sensory stimulation in the generation of pleasure, gratification, and tranquility. The imperative to generate sensory stimulation is so compelling that when it is deficient or absent, humans self-stimulate or hallucinate it. Thus, McCray[29] claimed that compulsive masturbation (10-15 times per day) in children was commonly related to withdrawal of affectionate parental tactile stimulation and was reversed by re-instatement of affectionate non-sexual tactile contact by the parents. The salience of sensory stimulation, certainly for humans, was dramatically demonstrated by Mason and Brady,[30] who created a sensory deprivation environment in which the participants sat with the lights out in an anechoic chamber, seated in a padded armchair, their feet cushioned. Within only 15 minutes, they experienced visual, auditory, and olfactory hallucinations. The authors concluded, "In the absence of external stimuli, perceptual distortions are presumably internally generated by the individual, and in addition are misattributed as external in origin...." This "internal" generation of neuronal activity as a compensatory response to its perceived absence has been proposed as a basis for some psychosomatic disorders.[31] As an example, there is extensive literature on the relation between alexithymia, which refers to the lack of awareness of, or lack of words for, feelings, and psychosomatic disorders, including asthma,[32-34] which generates intense sensation from the lung congestion. The sensory stimulation thereby generated has been suggested as a compensatory neuronal response to such lack of awareness of feelings, and the body's best remaining attempt to provide sensory stimulation—better than "nothing"—albeit pathological.[31] The examples cited above suggest the imperative of neuronal activation for physical and mental health, the negative consequences of its dearth or absence, and the positive, rewarding, pleasurable effects of sensory stimulation-induced neuronal activation.

NEURONAL INHIBITION IS THE COMPLEMENT OF NEURONAL EXCITATION: EXAMPLES OF THEIR CONCURRENT, COORDINATED ACTION

Neuronal Inhibition Enables Graceful, Non-spastic Movement

Neuronal inhibition plays a normal, adaptive role in behavior, from the most delicate to the most vigorous, adjusting to the intensity of the neuronal excitation. Without the inhibition, our movements at all intensities would be spastic. As represented in Figure 1, the precise, delicate finger movement required for moving a chess piece involves a relatively low intensity of neuronal excitation and a corresponding low intensity of inhibition. A stroll down the street involves a higher level of excitation and matching inhibition, maintaining our graceful, non-spastic movement. Running a race or running up a flight of stairs involves an even higher level of excitation and a matching higher level of inhibition. Thus, the intensity of inhibition, matched to the intensity of excitation, enables graceful, non-spastic movement at all intensities of muscular activity.

Neuronal Inhibition Enables Functional Coordination of Spinal Reflexes

Neuronal inhibition plays an essential, "hard-wired" role in even the simplest form of behavior: the spinal reflexes. In the simplest of the reflexes—the extensor ("knee-jerk") reflex—the input from a sensory nerve enters the spinal cord and synapses on one motor nerve that innervates the quadriceps muscle of the thigh. In response to an innocuous tap on the patellar (knee-cap) tendon, the quadriceps muscle contracts and extends the leg. Concurrently, a GABA-releasing inhibitory interneuron interposed between the sensory nerve and the motor nerve components controlling the ("antagonistic") flexor muscle of the thigh, inhibits the flexor muscle

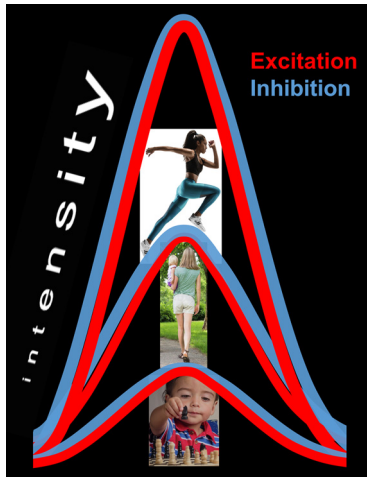

Figure 1. As the intensity of motoric excitation increases, so does that of motoric inhibition, thereby enabling precise, graceful, non-spastic motor activity at low intensity (eg, manipulating a chess piece), medium intensity (eg, strolling), and high intensity (eg, running). Thus, the intensity of neuronal inhibition is matched to the intensity of motor excitation. In this figure and that following, relative intensity of excitation and inhibition is represented as height and width of the areas; red and blue represent excitation and inhibition, respectively; time is represented on the x-axis. Figure 1 is available in color online at www.smr.jsexmed.org.

contraction, preventing it from competing with the extensor muscle contraction. In contrast with extensor reflexes, flexor (withdrawal) reflexes respond to noxious stimulation.[17] In that case, the antagonistic muscle that is inhibited is the extensor muscle. Absent the inhibition, both the flexor and the extensor muscles would contract simultaneously, oppose each other, and potentially tear their tendons. The role of GABA as the major inhibitory neurotransmitter of the motor system is evident not only for the reflexes, but also for the suppression of spasticity, as exemplified by the accepted therapeutic use of the GABA agonist, baclofen, administered via surgically implanted pump directly to the spinal cord, in cases of spinal cord injury.[35] Thus, excitation and inhibition work cooperatively, ensuring that flexors and extensors are reciprocally prevented from contracting simultaneously, enabling the evolutionarily adaptive motor response to the sensory stimulation.

Neuronal Inhibition Enables Multiple Components of Birth Canal Stimulation

In rats, gentle probing against the cervix, which also stretches the vagina, produces complete immobilization, accompanied by total blockage of the withdrawal reflex normally elicited by foot pinch, concurrently with intense facilitation of the extensor reflexes of lordosis and the legs.[36] The mechanical stimulation of the vagina and cervix (ie, the "birth canal") that elevates pain threshold during copulation in rats[37] may, during pregnancy and parturition even in humans, represent an evolutionarily adaptive mechanism that also attenuates pain, thereby reducing stress that could interfere with parturition, lactation, and bonding with the newborn.[38,39] Furthermore, the birth canal stimulation induces quiescent immobility, and can extend the hind legs and trunk, straightening the path of expulsion of the fetuses, thereby facilitating parturition, at least in some quadrupeds. The attenuation of stress of the mother during pregnancy has been shown to have a beneficial consequence for the normal neurological and behavioral development of the newborn.[40]

Neuronal Inhibition in Innocuous and Noxious Sensory Processing

The GABAergic inhibitory spinal cord interneurons produce a profound *sensory* inhibitory effect as well as their motor inhibitory effect. This prevents innocuous tactile stimulation from being painful, which is a pathological condition termed "allodynia." One example is that upon administration of the GABA receptor antagonist, bicuculline, directly into the subdural space of the spinal cord, rats exhibited an intense allodynia, in which case simply blowing gently on the fur resulted in prolonged stress vocalization and cowering.[6] This implies the existence of a normal GABAergic inhibition of innocuous tactile sensory activity, preventing allodynia.

Neuronal inhibition also plays a role in visual and other sensory systems, in the process of "lateral" inhibition, which sharpens perceived boundaries, preventing them from being blurry and indistinct (eg,[41,42]).

Neuronal Inhibition in Response to Vaginal Self-Stimulation Attenuates Pain in Women

Most germane to the present discourse, excitation generated by vaginal self-stimulation in women activated concurrent inhibition of pain; the intensity of the pain inhibition increased as the perceived intensity of the excitation increased. Pain threshold was measured using an instrument that produced increasing calibrated compressive force on the fingers, recording the force when it was reported as painful. When the women applied continuous pressure to their anterior vaginal wall using a passive dildo, their pain thresholds increased from their unstimulated baseline by about 45%. However, when the women applied the continuous vaginal stimulation in a way to make it feel pleasurable, their pain thresholds increased by about 70% and continued to increase to 85% over the next 5 minutes. Continuing the stimulation, four of the 10 women then experienced orgasms in response to the self-stimulation, at which time their pain thresholds increased by over 100%.[2] Thus, as the intensity of excitation increased from pressure to pleasure to orgasm, the intensity of induced inhibition of the pain increased concurrently. The greater the vaginal sensory stimulation-induced excitation, the greater the inhibition of pain perceived at the fingers, physically remote from the source of stimulation.[2]

Neuronal Inhibition Enables Orgasm

We propose that the inhibition elicited by genital stimulation does more than inhibit pain; it *enables* the excitation to increase in intensity to orgasmic levels without becoming aversive. As the genital stimulation-induced excitation intensity increases, it stimulates an increase in the inhibition intensity, and thereby raises the pain threshold.[2] In this manner, the increasing inhibition maintains its control of the increasing excitation, enabling the excitation intensity to increase to the pleasurable intensity of orgasm without becoming aversive or painful.

The concept of "pain threshold" implies that if the threshold is exceeded, the sensory stimulation related to the threshold is perceived as aversive or painful. As an example, high intensity sensory stimulation can itself activate the endogenous pain-blocking system,[43] thereby raising the pain threshold. But if the intensity of the sensory stimulation is so intense that the capacity of the endogenous pain-blocking system is insufficient to block it, the elevated pain threshold is nevertheless exceeded and, by definition of the "pain *threshold*," pain is perceived. Genital stimulation can gradually increase in intensity without exceeding the pain threshold, thereby enabling it to be perceived as not aversive or painful, up to the high intensity of orgasm, which is perceived as pleasurable.

In Figure 2, we schematically represent our proposal that in the case of orgasm, as the excitation level and inhibition level increase jointly and concurrently, the excitation level increases, recruiting more and more neurons, both excitatory and inhibitory, to a point at which the inhibition level no longer prevents the excitation from becoming aversive. That critical point, which may be at just the verge of feeling aversive, we propose to be the orgasmic "climax," which triggers not only the high threshold autonomic sympathetic ejaculation mechanism in men[44] and probably in women, but also continues to stimulate the inhibitory neuronal response. The difference between women's and men's orgasm may be in the pattern and time course of the inhibition that is triggered by the orgasm. Perhaps the inhibition triggered by orgasm in men suppresses the excitation immediately after the orgasm more abruptly than in women, then the inhibition persists,[45] predominating over the excitation and resulting (with some exceptions in the case of multi-orgasms in men[46]), in the refractory period. In contrast in women, the triggered inhibition, rather than suppressing the excitation to a refractory level, may wax and wane in intensity. This could enable the excitation to fluctuate, wavelike, to subsequent, in some cases higher, orgasmic intensities, which could occur repeatedly, accounting for multiple orgasms. Multiple orgasms are more common in women (eg, 39/100 health professionals)[47] than in men (eg, < 10% in a meta-analysis.)[48]

MOTOR AND SENSORY COMPONENTS OF ORGASM

Contribution of Muscle Proprioception to Orgasmic Pleasure

In their classic book of 1953, Kinsey et al[49] stated, "One of the most striking aspects of sexual performance is the development of neuromuscular tensions throughout the body of the responding individual, female or male. From head to toes, the muscles contract and relax involuntarily in steady or more convulsive rhythms (p. 618)." Subsequently, many authors have referred to the occurrence and feeling of elevated muscle tension as playing a significant role in the generation, intensification, and thereby pleasurable quality of orgasm. This pleasure-generating proprioception[25] is generated not only by the contraction of musculature of the uterus and vagina, but also pelvis, pelvic floor, abdomen, legs, feet, arms, neck, jaw, and face.[50-54] As genital stimulation continues and orgasm approaches, there is a widespread buildup of muscle tension that reaches a peak at orgasm. The observations that muscle trembling often occurs, and that extensor activity may predominate, as in toe extension or curling and arching of the back,[49] is evidence that both flexors and extensors become activated concurrently or alternate rapidly. This may represent a reduced level of function of the spinal cord

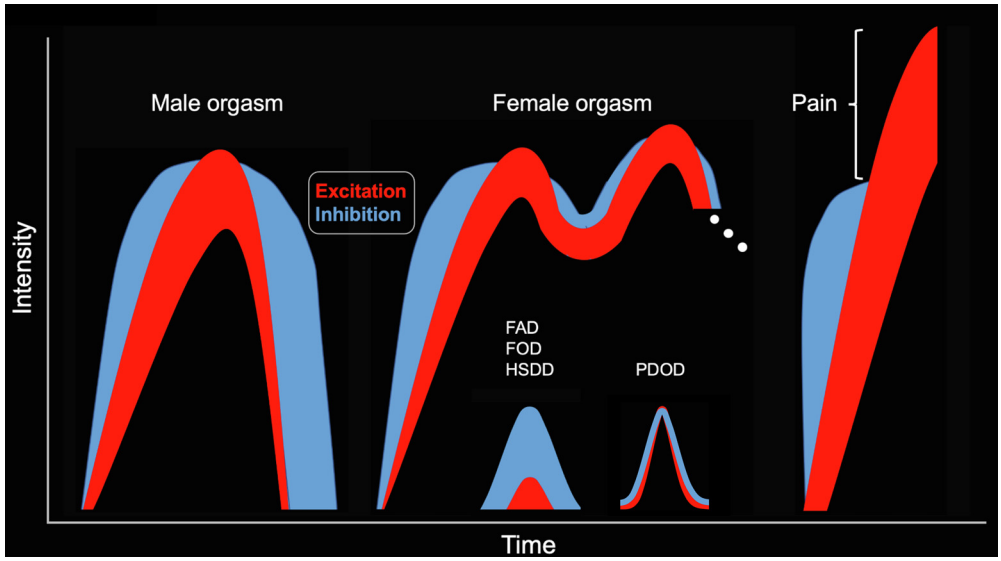

Figure 2. The proposed role of neuronal excitation and inhibition in orgasm and pain. We postulate that inhibition enables excitation to reach high intensity without becoming aversive. However, at the orgasmic climax, the excitation intensity exceeds the inhibition intensity and is just at the verge of aversive intensity. "Characteristic" orgasm in males (left side of figure) is conceptualized as the peak excitation intensity exceeding the inhibition intensity sufficient to surpass and trigger the high threshold sympathetic autonomic control of ejaculation, and also an intense prolonged neuronal inhibition that abruptly decreases the excitation, thereby generating the refractory period. By comparison, in "characteristic" female orgasm (mid-figure), ejaculation may be triggered, and the post-orgasm inhibition is less intense than in males. Thus, the excitation is not as abruptly decreased as in the male, and it may continue in conjunction with inhibition, even reaching a higher subsequent intensity in successive waves before decreasing. The pathologies, FAD, FOD, and HSDD (mid-figure, lower part) are conceptualized as due to a low level of excitation and/or a high level of inhibition, both of which result in excitation failing to increase to pleasurable intensity. In the case of orgasmic anhedonia (PDOD), we conceptualize a too-low intensity of inhibition, which allows the excitation to generate an orgasm at an intensity that is too low to generate sexual pleasure. At the right side of the figure, under conditions in which the excitation level clearly exceeds the inhibition level, the net effect is aversive, perceived as pain. FAD = female arousal disorder; FOD = female orgasmic disorder; HSDD = hypoactive sexual desire disorder; PDOD = pleasure dissociative orgasmic disorder.

inhibitory interneuron system that during reflex responses prevents antagonistic muscles from contracting, thus enabling antagonistic muscles to contract concurrently or in rapid alternation. This type of spasticity is likely due to inhibition of the classic brainstem-descending motor-inhibitory system first characterized by Magoun,[55] which accounts for the spasticity that occurs in persons in whom there is traumatic disconnection of the descending pathways from brainstem to spinal cord.

The Sensory Qualities of Orgasm are Comparable in Women and Men

The above are descriptions of the orgasmic process mainly from the objective, physiological, neurological perspective. Regarding the subjective quality, Vance and Wagner[56] reported that sexuality experts were not able to discern whether the subjective descriptions that they evaluated were written by men or women, when the references to specific genital components were edited out of the texts.

Neurophysiological "Recruitment" and "Windup" Underlying Orgasm

Orgasm can be described as a buildup of sensory, muscular, and imagery excitation and tension, reaching a climax, and then satisfaction, resolution, tranquility, rest; recurrent similar waves may be elicitable, that can be stronger than the first.[57] The buildup of neuronal excitation resulting from repetitive sensory stimulation utilizes a process of "recruitment," which brings increasing numbers of neurons into activity. It leads to a well-recognized neurophysiological process, termed "windup,"[58] which requires the joint, coordinated activation of excitatory and inhibitory neurons.[59]

Orgasm and Pain Share the Same Neural System

The Spinothalamic Tract Mediates Both Pain and Orgasm. It is noteworthy that the same (spinothalamic) neural pathway to the brain that conveys pleasurable vaginal sensation, also conveys pain. This was demonstrated in an analysis of more than 90 women and men with spinal cord injury at various levels. Beric and Light[60] reported that 2 of the women and 3 of the men had injuries that completely blocked their sense of pain, but did not affect their sense of touch below the level of their injury. The sense of touch is carried via a separate pathway—the dorsal column system—which in their cases remained intact after their spinal cord injury. In each of the 5 cases, the patients had completely lost not only their sense of pain below the level of their injury, but they also lost the ability to experience orgasm from genital stimulation! The investigators asked the patients to apply genital self-stimulation with a vibrator using as much force as possible, which they could feel (via their intact dorsal column system), but they still failed to experience orgasms, although they all had been normally orgasmic prior to their spinal cord injury. The authors concluded that these patients had suffered selective complete injury to the spinothalamic (anterolateral) tract. Thus, both pain and the sensory activity generated by genital stimulation leading to orgasm is conveyed by the same, spinothalamic, tract.

Suggestive supporting evidence that orgasm and pain share a common neural system is from a communication from a patient after undergoing a prostatic artery embolization for benign prostatic hypertrophy (I. Goldstein, personal communication). The patient described a stinging feeling in his urethra while urinating that was "intense for the first 3 days," then gradually subsided and ceased after the second week. The patient described that starting on day 4 and continuing through the end of the second week, he experienced persisting orgasms that could last for several days at a time. Both the persistent orgasms and the urethral pain then ceased jointly at the end of two weeks. Perhaps initially, when the patient's pain was so intense, it superseded and interfered with his orgasms, but then, when the pain continued at a lower intensity but persisted, the orgasms started; then both ceased jointly after 2 weeks. This also implies that his threshold for pain was lower than that for orgasm. This patient's observations are consistent with the evidence reported by Beric and Light,[60] above, that orgasm and pain share the same sensory neural pathway, which in this patient was likely activated via pelvic nerve afferents.

Brain Regions that Mediate Both Pain and Orgasm. The spinothalamic tract conveys noxious-intensity afferent activity to the thalamus, which relays projections to the insula, anterior cingulate cortex, amygdala, PAG (PeriAqueductal Gray), and raphé,[61] brain regions that are activated by pain.[62] Based on functional Magnetic Resonance Imaging (fMRI), we reported that each of these same brain regions is also significantly activated during orgasm in women.[63,64] The brain activity occurring during the 20 seconds immediately preceding the moment that the women pressed a button indicating the start of their orgasm, was electronically subtracted from the brain activity occurring during the 20 seconds of the orgasm that immediately followed their button press. This computation thus filtered out the high arousal activity immediately preceding orgasm from the activity during orgasm, thereby revealing brain regions whose activation was selective to orgasm. The brain regions classically activated by pain that were specified above, were also selectively activated during orgasm, that is, insula, anterior cingulate cortex, amygdala, PAG, and raphé. The latter two brain regions comprise a major component of the brainstem-to-spinal cord descending serotonergic and noradrenergic system, which activates inhibitory interneurons that block incoming nociceptive (ie, pain-producing) activity.[5] We reported that in rats, vaginal stimulation which, as noted above, produces a profound inhibition of responses to noxious stimulation, releases serotonin and norepinephrine into superfusates of the spinal cord, evidence that this descending brainstem-spinal cord system is indeed activated by vaginal stimulation.[65] This is most likely a major component of the mechanism underlying the pain-inhibitory effect of vaginal stimulation in women.

There are additional shared properties of orgasm and pain. They both generate a high level of activation of the sympathetic division of the autonomic nervous system, as indicated by tachycardia, hypertension, sweating, and pupil dilatation.[66] And both orgasm and pain can produce a pattern of intense facial grimace and vocalization that is similar between the 2 conditions.[49]

While the orgasm and the pain mechanisms share the above morphological and functional similarities, obviously one is pleasurable and the other is aversive. An explanation of this seeming paradox is the possible existence of local inhibitory interneuron links between the orgasm activation and the pain activation, in at least some of these common brain regions, for example, insula, amygdala, and/or anterior cingulate cortex, where the orgasm activation could actively inhibit the neurons otherwise activated by pain. Consistent with this, levels of the inhibitory neurotransmitter, GABA, were found in the anterior insula in lower concentrations in patients with a chronic pain syndrome (fibromyalgia) than in a healthy comparison group.[67] This provides a neurotransmitter basis for a GABAergic pain-inhibitory system in a cortical region (insula) that is activated by orgasm. While current functional MRI methodology that we used in our reported studies cannot distinguish between active inhibition and active excitation, it is possible that future analysis using the method of effective connectivity, which computes cross-correlation of activity between pairs of selected brain regions,[68] in brain regions activated by orgasm and by pain within each individual, could provide insight into the neural mechanism underlying orgasm-induced inhibition of pain.

Orgasm as a Ubiquitous Property of the Nervous System: Non-Genital Orgasms

As previously proposed,[69] genital stimulation-induced orgasm can be considered as but a special case of a ubiquitous neuronal "orgasmic process." There exists a plethora of non-genital orgasms that can be elicited from diverse bodily regions, for example, hand, shoulder, mouth, breasts, anus, toes, each of which involves a buildup of excitement typically including muscle tension to a climax and then resolution. These include specific "orgasmic" motor patterns, for example, a sneeze, a yawn, stretching. They can be of lower intensity as well, for example, the "event" of the start and completion of urinating or defecating, or scratching and satisfying an itch. These each represent a buildup to an "event" and its resolution. The "event" (ie, the "orgasm" or "climax") in these examples occurs at a low intensity relative to the intensity of genital stimulation-induced orgasm, but they would all also involve linked intensities of excitation and inhibition.

Orgasms elicited non-physically, by thinking. The ability to generate physiologically-verified orgasms from thought alone, without applying physical stimulation, as reported based on 10 women,[66] raises the question of the role of neuronal inhibition in that process. It is probable that the ability to have a physiological orgasm from thought alone requires the prior experience of genital physical stimulation-elicited orgasms and the present memory of them. Then the physiological generation of the thought-induced orgasm would likely involve actual neuronal excitation and inhibition, which would thereby enable the orgasm-characteristic elevation in pain threshold, heart rate, blood pressure, and pupil diameter reported in these women, perhaps involving increased muscle tension, which was not measured.

CONCEPTS OF SEXUAL RESPONSE PATHOLOGIES BASED ON EXCITATION AND INHIBITION

Female Sexual Interest/Arousal Disorder (HSDD/FAD)

The characterization of the conditions termed, "hypoactive sexual desire disorder" (HSDD) and "female arousal disorder" (FAD) in the DSM-4,[70] were revised in the DSM-5 with the encompassing term, "female sexual interest and/or arousal disorder."[71-73] This condition is characterized in the DSM-5 as: "lack of, or significantly reduced, sexual interest and/or arousal, as manifested by at least 3 of the following: (i) absent and/or reduced interest in sexual activity, (ii) absent and/or reduced sexual and/or erotic thoughts or fantasies, (iii) no and/or reduced initiation of sexual activity, and typically unreceptive to a partner's attempts to initiate, (iv) absent and/or reduced sexual excitement and/or pleasure during sexual activity in almost all or all sexual encounters, and (v) absent and/or reduced sexual interest and/or arousal in response to any internal or external sexual and/or erotic cues."

Parish and Hahn[13] characterized the etiology of HSDD concisely: "HSDD is described dynamically as an imbalance in the relationship of sexual excitatory and inhibitory processes which are independent of one another and determine sexual response. Inhibitory factors include life situation and relationship factors, personal sexual beliefs and related behaviors, and biological factors, including comorbid medical and mental disorders, medications, and substance use." Thus, the authors conceptualized convergence of biological and psychological factors as the inhibitory neuronal basis for HSDD.

Perelman[12,16,74,75] formulated a concept of excitation and inhibition of sexual response, which he termed, the "Tipping Point" model, in the form of a metaphor of an old-fashioned balance, in which, see-saw-like, the left side goes up for excitation (sexual response, excite, "hot" in the model) while the right side for inhibition goes down (sexual response, inhibit, "not" in the model). In pathological conditions such as HSDD, they reverse—the inhibitory right side goes up (increases) while the excitatory left side goes down (decreases). The model omits the consideration that the intensities of both excitation and inhibition, at least in neurological terms, can both increase or decrease jointly and concurrently.

While this model can account for some of the above conditions based on predominant inhibition, it seems less applicable to those in which excitation and inhibition most likely covary. Pfaus[76] provided a neuropharmacological basis for the Perelman model, with evidence of the role of the various excitatory (norepinephrine, dopamine, oxytocin, melanocortins) and inhibitory (opioids, endocannabinoids, serotonin) neurotransmitters distributed on the excitatory and/or inhibitory sides of the scale. However, that model also does not address the likely covariance of excitatory and inhibitory neurotransmitter function in relation to the specific conditions. In the model of Bloemers et al,[15] 2 factors are proposed to account for HSDD: increased level of inhibition and increased insensitivity to sexual cues. Their model proposes that excitation can trigger inhibition, but in a negative sense; that is, persons with high sensitivity to sexual stimuli may be particularly susceptible to negative sexual experience, which could elicit a high level of activation of a sexual inhibitory process, and thereby HSDD. And those persons with a low sensitivity to sexual stimuli would have decreased levels of activation of sexual excitatory processes, resulting in low sexual desire. Their concept is similar to the other concepts of sexual response, in viewing excitation and inhibition solely as increasing or decreasing sexual response.

Female Orgasmic Disorder (FOD)

The DSM-5 characterizes "female orgasmic disorder" (FOD) as a significant change in orgasm such as delay, reduction of intensity or frequency, or cessation of orgasm.[72] HSDD, FOD, and FAD may each result from an excessively low level of excitation, and/or an excessively high level of inhibition. Both the low level of excitation and the high level of inhibition or both can result from a multitude of factors, including psychological and/or experiential, physical, and pharmacological. Meston and Bradford (p.20)[77] stated, "Although there is no known biological cause of FOD, a number of medical conditions lead to orgasm difficulties in women, and side effects of a number of pharmacological treatments include impairments in orgasm function." We have represented our concept of the relative roles of neuronal excitation and inhibition in FOD, HSDD, and FAD schematically in Figure 2.

Orgasmic Anhedonia or "Pleasure-Dissociative Orgasmic Disorder (PDOD)"

The condition in which individuals who experience orgasms but do not derive pleasure from the orgasms has been characterized as "orgasmic anhedonia," and termed "Pleasure-Dissociative Orgasmic Disorder" (PDOD).[78] There are multiple forms of anhedonia in addition to sexual or orgasmic anhedonia, which have been variably conceptualized[79,80] in terms of e.g., brain structure,[81] brain activity via functional Magnetic Imaging,[82] and pharmacological therapies.[83-86] But to our knowledge, none of the various forms of anhedonia, including orgasmic anhedonia, has been interpreted in terms of the relative roles of excitatory and inhibitory neuronal processes.

It is likely that orgasmic anhedonia (PDOD) differs in etiology from female sexual interest and/or arousal disorder or female orgasmic disorder; it may result from an excessively *low* level of inhibition. That is, if the level of inhibition does not increase sufficiently as the level of excitation rises, then the excitation intensity could soon surpass the inhibitory intensity, and "trickle out" into a low intensity orgasm. One patient described this as "I wanted a mountain and got an anthill" (I. Goldstein, personal communication). High intensity excitation, at least in the sexual context, evidently can be more pleasurable than low intensity excitation. In Figure 2 we represent our concept that this pleasure dissociative orgasmic disorder (PDOD) results from too *low* a level of inhibition.

Premature ejaculation (PE) is perhaps a form of orgasmic anhedonia. Evidence for PE being a consequence of a too-low level of inhibition is that SSRIs, which are well-known to inhibit sexual response in women and men[87] may be used effectively off-label to delay the PE.[88] Based on such evidence, an effective treatment for PDOD may be administration of a low dose of a short-acting SSRI prior to sexual activity, titrating the dose to gradually increase the level of this inhibitory factor. The rationale for this treatment is to enable an increase in the intensity of inhibition and thereby elevate the orgasm threshold, which when surpassed, may generate a more intense orgasm with concomitant greater pleasure, overcoming the anhedonia.

Persistent Genital Arousal Disorder and/or GenitoPelvic Dysesthesia (PGAD/GPD)

Sandra Leiblum, who first characterized PGAD (eg,[89]) recognized that "…awareness of sensations of genital arousal is quite normal for some women and may be experienced as mildly pleasurable or mildly annoying…(but)…in order to qualify for a diagnosis of PGAD, there must be accompanying feelings of distress…." In recognition of the abnormality of sensations associated with PGAD, the definition was expanded in a consensus conference at which PGAD/GPD was characterized by "…persistent or recurrent, unwanted or intrusive, distressing feelings of genital arousal or being on the verge of orgasm (genital dysesthesia), not associated with concomitant sexual interest, thoughts, or fantasies….."[10] There are multiple etiologies recognized for PGAD/GPD, that include pathologies of the genitals, lumbosacral nerve roots (eg, Tarlov cysts[90]) and/or herniated intervertebral discs, brain, and/or psychosocial factors.[10] It is likely that the distressing, confounded relation between normally pleasurable genital sensations and aversive genital sensations is a function of uncontrollable fluctuation between genital afferent excitatory and inhibitory activity, in which the level of inhibitory activity at times is insufficient to prevent the excitatory activity from reaching aversive, and even painful, intensity. While we interpret both PGAD and PDOD as both involving too-low

levels of neuronal inhibition relative to that of the neuronal excitation, they differ greatly in the intensity of the underlying excitation. The anatomical pathologies in PGAD generate intense neuronal excitation, for which the induced inhibition does not attenuate the aversive quality of the excitation. In contrast, the intensity of neuronal excitation in PDOD is conceptualized as being low, while the related inhibition is still lower, resulting in a low-intensity excitatory peak over the inhibition, resulting in the perception that the orgasm is weak.

PAIN: THE POINT AT WHICH EXCITATION EXCEEDS INHIBITION

In our concept of the dynamic relation between excitatory and inhibitory neuronal activity, even beyond the realm of sexual response, excitation would feel pleasurable so long as the inhibition is of an intensity sufficient to prevent the excitation from becoming aversive. However, if and when the excitation intensity does exceed the inhibitory intensity, we would perceive the excitation as aversive or painful. Even when the excitation intensity becomes painful, it still activates the pain-inhibitory systems (eg,[43]), which are variably effective in intensifying the inhibition to counteract the excitation. The efficacy of the inhibition varies, contingent on the source, nature, and intensity of the excitation. When the aversive and/or pain threshold is exceeded, pain is experienced and withdrawal responses, physical and/or cognitive, are triggered.

CONCLUSION

It is important to recognize that there is normally a continuous dynamic, changing balance between excitatory and inhibitory neuronal activity in the brain as well as in the spinal cord. Inhibitory processes, which are essential, continuous, and integral to neuronal function, not only counteract excitatory processes, but can *enable* sensory stimulation of excitatory processes to increase in intensity to the verge of becoming aversive, as in the case of pleasurable orgasm. In sexual response, if genital stimulation leads to just a low level of excitation, and/or inhibitory processes attenuate the level of excitation elicited by genital stimulation, both of these conditions may result in female sexual interest and/or arousal disorder, and/or orgasmic disorders. If the inhibitory intensity is too low, the excitation elicited by genital stimulation may be perceived as aversive at a relatively low level, leading to orgasm of low intensity and hence minimally pleasurable. This may be perceived as orgasmic anhedonia (pleasure-dissociative orgasmic disorder). At excitation intensities that exceed the inhibition intensity, the difference may be perceived as aversive or painful.

We suggest that the increase in perceived excitation leading to orgasm is generated in large part by the increasing intensity of muscle contraction throughout the body. Thus, to the extent that intense bodily muscular contraction (ie, exertion) is an essential component of orgasm, even to the verge of pain, the neural systems are congruent that mediate the muscle tension of orgasm and proprioception, including proprioceptive pain. The intense muscular exertion throughout the body leading to orgasm is also expressed in the characteristic facial grimace of orgasm. It is likely that the same muscle tension-induced proprioceptive orgasmic process accounts for the great variety of "non-genital orgasms," described as elicitable from essentially any region of the body. Thus, we suggest that the "orgasmic process," of which genital stimulation-induced orgasm is a special case, is a property of the same neural system that mediates proprioceptive pain.

We are designed to actively seek and generate sensory stimulation as a primary life process. To the degree that sensory stimulation elicits activation that is non-aversive, we perceive it as pleasurable, and the higher the non-aversive intensity is, the more pleasurable. Thus, our continual seeking and acquisition of such stimulation is a fundamental imperative that ensures the survival of our neurons, ourselves, and our species.

ACKNOWLEDGMENTS

We gratefully acknowledge Celeste Bittoni, MS, for her constructive comments on this manuscript.

Corresponding Author: Barry Komisaruk, PhD, Psychology, Rutgers University, 101 Warren St, Newark, New Jersey 07102, USA, Tel: 973 462 0178; Fax: 973 353 1171; E-mails: brk@psychology.rutgers.edu, brk@rutgers.edu

Conflict of Interest: The authors report no conflicts of interest.

Funding: This research was supported in part by grants PGC2018-094919-B-C21 and PID2021-127547-NB-C21 from the Spanish Ministry of Science and Innovation (MCRC).

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and design: B.R.K., M.C.R.D.C

(b) Acquisition of data: B.R.K., M.C.R.D.C

(c) Analysis and interpretation of data: B.R.K., M.C.R.D.C

Category 2

(a) Drafting the manuscript: B.R.K., M.C.R.D.C

(b) Revising it for intellectual content: B.R.K., M.C.R.D.C

Category 3

(a) Final approval of the completed manuscript: B.R.K., M.C.R.D.C

REFERENCES

1. Bowery NG, Smart TG. GABA and glycine as neurotransmitters: a brief history. **Br J Pharmacol 2006;147(Suppl 1): S109–S119 PMID: 16402094; PMCID: PMC1760744. doi: 10.1038/sj.bjp.0706443.**

2. Whipple B, Komisaruk BR. Elevation of pain threshold by vaginal stimulation in women. **Pain 1985;21:357–367 PMID: 4000685. doi:** 10.1016/0304-3959(85)90164-2.
3. Swanson OK, Maffei A. From hiring to firing: activation of inhibitory neurons and their recruitment in behavior. **Front Mol Neurosci 2019;12:168. PMID: 31333413; PMCID: PMC6617984. doi:** 10.3389/fnmol.2019.00168.
4. Jelitai M, Puggioni P, Ishikawa T, et al. Dendritic excitation-inhibition balance shapes cerebellar output during motor behaviour. **Nat Commun 2016;7:13722. PMID: 27976716; PMCID: PMC5172235. doi:** 10.1038/ncomms13722.
5. Basbaum AI, Fields HL. The origin of descending pathways in the dorsolateral funiculus of the spinal cord of the cat and rat: further studies on the anatomy of pain modulation. **J Comp Neurol 1979;187:513–531 PMID: 489790. doi:** 10.1002/cne.901870304.
6. Roberts LA, Beyer C, Komisaruk BR. Nociceptive responses to altered GABAergic activity at the spinal cord. **Life Sci 1986;39:1667–1674 PMID: 3022091. doi:** 10.1016/0024-3205(86)90164-5.
7. Prescott SA. Synaptic inhibition and disinhibition in the spinal dorsal horn. **Prog Mol Biol Transl Sci 2015;131:359–383 Epub 2015 Jan 30. PMID: 25744679. doi:** 10.1016/bs.pmbts.2014.11.008.
8. Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. **Physiol Rev 2009;89:707–758 PMID: 19342617. doi:** 10.1152/physrev.00025.2008.
9. Lolignier S, Eijkelkamp N, Wood JN. Mechanical allodynia. **Pflugers Arch 2015;467:133–139 Epub 2014 May 22. PMID: 24846747; PMCID: PMC4281368. doi:** 10.1007/s00424-014-1532-0.
10. Goldstein I, Komisaruk BR, Pukall CF, et al. International society for the study of women's sexual health (ISSWSH) review of epidemiology and pathophysiology, and a consensus nomenclature and process of care for the management of persistent genital arousal disorder/genito-pelvic dysesthesia (PGAD/GPD). **J Sex Med 2021;18:665–697 Epub 2021 Feb 19. PMID: 33612417. doi:** 10.1016/j.jsxm.2021.01.172.
11. Kaplan HS. Sexual desire disorders: dysfunctional regulation of sexual motivation. New York, NY: Brunner/Mazel, Inc; 1995
12. Perelman MA. The sexual tipping point: a mind/body model for sexual medicine. **J Sex Med 2009;6:629–632 Epub 2009 Feb 6. PMID: 19210711. doi:** 10.1111/j.1743-6109.2008.01177.x.
13. Parish SJ, Hahn SR. The Epidemiology and Diagnosis of Hypoactive Sexual Desire Disorder and Causes of HSDD: Situational, Depression, Drugs, Chronic Illnesses, and Hormonal Depletion. In: Lipshultz, L. I., Pastuszak, A. W., Goldstein, A. T., Giraldi, A.,
14. Bancroft J, Graham CA, Janssen E, et al. The dual control model: current status and future directions. **J Sex Res 2009;46:121–142 PMID: 19308839. doi:** 10.1080/00224490902747222.
15. Bloemers J, van Rooij K, Poels S, et al. Toward personalized sexual medicine (part 1): integrating the "dual control model" into differential drug treatments for hypoactive sexual desire disorder and female sexual arousal disorder. **J Sex Med 2013;10:791–809 Epub 2012 Nov 6. PMID: 23130782. doi:** 10.1111/j.1743-6109.2012.02984.x.
16. Perelman MA. Psychosexual therapy for delayed ejaculation based on the sexual tipping point model. **Translational andrology and urology 2016;5:563.**
17. Schneirla TC. Aspects of stimulation and organization in approach/withdrawal processes underlying vertebrate behavioral development. Advances in the study of behavior, 1. New York, NY: Academic Press; 1965. p. 1–74.
18. Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. **J Neurophysiol 1963;26:1003–1017 PMID: 14084161. doi:** 10.1152/jn.1963.26.6.1003.
19. Conforti L, Gilley J, Coleman MP. Wallerian degeneration: an emerging axon death pathway linking injury and disease. **Nat Rev Neurosci 2014;15:394–409 PMID: 24840802. doi:** 10.1038/nrn3680.
20. Montoya-Filardi A, García-Junco Albacete M, Ortolá Fortes P, et al. Imaging secondary neuronal degeneration. **Radiologia (Engl Ed) 2022;64:145–155 PMID: 35504680. doi:** 10.1016/j.rxeng.2022.01.001.
21. Van De Meent H, Hosman AJ, Hendriks J, et al. Severe degeneration of peripheral motor axons after spinal cord injury: a European multicenter study in 345 patients. **Neurorehabil Neuronal Repair 2010;24:657–665 Epub 2010 May 3. PMID: 20439500. doi:** 10.1177/1545968310368534.
22. Eidelberg E, Nguyen LH, Polich R, et al. Transsynaptic degeneration of motoneurones caudal to spinal cord lesions. **Brain Res Bull 1989;22:39–45 PMID: 2713715. doi:** 10.1016/0361-9230(89)90125-1.
23. Sugimoto T, Bennett GJ, Kajander KC. Transsynaptic degeneration in the superficial dorsal horn after sciatic nerve injury: effects of a chronic constriction injury, transection, and strychnine. **Pain 1990;42:205–213 PMID: 2247318. doi:** 10.1016/0304-3959(90)91164-E.
24. Ramachandran VS, Blakeslee S. Phantoms in the brain: human nature and the architecture of the mind. New York, NY: HarperCollins; 1998.
25. Glickman SE, Schiff BB. A biological theory of reinforcement. **Psychological review 1967;74:81.**
26. Del Cerro MCR. El cerebro afectivo. Barcelona: Plataforma Editorial; 2017.
27. Kaufman IC. Some theoretical implications from animal behaviour studies for the psycho-analytic concepts of instinct, energy, and drive. **Int J Psycho-Anal 1960;41:318.**
28. Fromm E. The art of loving: an enquiry into the nature of love. New York, NY: Harper; 1956.
29. McCray GM. Excessive masturbation of childhood: a symptom of tactile deprivation? **Pediatrics 1978;62:277–279.**
30. Mason OJ, Brady F. The psychotomimetic effects of short-term sensory deprivation. **J Nerv Ment Dis 2009;197:783–785 PMID: 19829208. doi:** 10.1097/NMD.0b013e3181b9760b.

31. Komisaruk BR. Visceral-Somatic Integration in Behavior Cognition, and "Psychosomatic" Disease. Advances in the study of behavior, 12. New York, NY: Academic Press; 1982. p. 107–140.
32. Weiner H. Psychobiology and human disease. Amsterdam: Elsevier; 1977.
33. Mattila AK, Kronholm E, Jula A, et al. Alexithymia and somatization in general population. **Psychosom Med 2008;70:716–722 Chicago.**
34. Khosravani V, Alvani A, Bastan FS, et al. The alexithymia, cognitive emotion regulation, and physical symptoms in Iranian asthmatic patients. **Pers Individual Differences 2016;101:214–219.**
35. Lake W, Shah H. Intrathecal baclofen infusion for the treatment of movement disorders. **Neurosurg Clin N Am 2019;30:203–209 Epub 2019 Feb 18. PMID: 30898271. doi:** 10.1016/j.nec.2018.12.002.
36. Komisaruk BR, Diakow C. Lordosis reflex intensity in rats in relation to the estrous cycle, ovariectomy, estrogen administration and mating behavior. **Endocrinology 1973;93:548–557 PMID: 4737236. doi:** 10.1210/endo-93-3-548.
37. Gómora P, Beyer C, González-Mariscal G, et al. Momentary analgesia produced by copulation in female rats. **Brain Res 1994;656:52–58 PMID: 7804845. doi:** 10.1016/0006-8993(94)91365-x.
38. Gintzler AR, Komisaruk BR. Analgesia is produced by uterocervical mechanostimulation in rats: roles of afferent nerves and implications for analgesia of pregnancy and parturition. **Brain Res 1991;566:299–302 PMID: 1814546. doi:** 10.1016/0006-8993(91)91713-b.
39. Whipple B, Josimovich JB, Komisaruk BR. Sensory thresholds during the antepartum, intrapartum and postpartum periods. **Int J Nurs Stud 1990;27:213–221 PMID: 2379982. doi:** 10.1016/0020-7489(90)90036-i.
40. Del Cerro MCR, Ortega E, Gómez F, et al. Environmental prenatal stress eliminates brain and maternal behavioral sex differences and alters hormone levels in female rats. **Horm Behav 2015;73:142–147 Epub 2015 Jul 7. PMID: 26163152. doi:** 10.1016/j.yhbeh.2015.07.004.
41. Francis G. Cortical dynamics of lateral inhibition: metacontrast masking. **Psychol Rev 1997;104:572–594 PMID: 9243965. doi:** 10.1037/0033-295x.104.3.572.
42. Yeonan-Kim J, Bertalmío M. Retinal Lateral Inhibition Provides the Biological Basis of Long-Range Spatial Induction. **PLoS One 2016;11:e0168963 PMID: 28030651; PMCID: PMC5193432. doi:** 10.1371/journal.pone.0168963.
43. Tobaldini G, Andersen EOL, Polato JJ, et al. Pain and stress: functional evidence that supra-spinal mechanisms involved in pain-induced analgesia mediate stress-induced analgesia. **Behav Pharmacol 2020;31:159–167 PMID: 31860563. doi:** 10.1097/FBP.0000000000000529.
44. Monnier M. Functions of the nervous system Vol. 1: autonomic functions. New York: Elsevier; 1968.
45. Allen K, Komisaruk BR. fMRI representation of erotic vs nonerotic genital self- stimulation; attenuation during the postorgasmic refractory period in men. Society for Neuroscience Annual Conference. 235.06/DD10; 2016.
46. Whipple B, Myers BR, Komisaruk BR. Male multiple ejaculatory orgasms: a case study. **J Sex Educ Ther 1998;23:157–162.**
47. Kratochvíl S. Opakovaný orgasmus u zen [Multiple orgasms in women]. **Cesk Psychiatr 1993;89:349–354 CzechPMID: 8124735.**
48. Wibowo E, Wassersug RJ. Multiple orgasms in men-what we know so far. **Sex Med Rev 2016;4:136–148 Epub 2016 Feb 5. PMID: 27872023. doi:** 10.1016/j.sxmr.2015.12.004.
49. Kinsey AC, Pomeroy WB, Martin CE, et al. Sexual behavior in the human female. Philadelphia: W.B. Saunders; 1953.
50. Messé MR, Geer JH. Voluntary vaginal musculature contractions as an enhancer of sexual arousal. **Arch Sex Behav 1985;14:13–28 PMID: 3977582. doi:** 10.1007/BF01541349.
51. Giuliano F, Rampin O, Allard J. Neurophysiology and pharmacology of female genital sexual response. **J Sex Marital Ther 2002;28(Suppl 1):101–121 PMID: 11898692. doi:** 10.1080/00926230252851230.
52. Meston CM, Levin RJ, Sipski ML, et al. Women's orgasm. **Annu Rev Sex Res 2004;15:173–257 PMID: 16913280.**
53. Pfaus JG, Quintana GR, Mac Cionnaith C, et al. The whole versus the sum of some of the parts: toward resolving the apparent controversy of clitoral versus vaginal orgasms. **Socio Affect Neurosci Psychol 2016;6:32578. PMID: 27791968; PMCID: PMC5084726. doi:** 10.3402/snp.v6.32578.
54. Bischof-Campbell A, Hilpert P, Burri A, et al. Body movement is associated with orgasm during vaginal intercourse in women. **J Sex Res 2019;56:356–366 Epub 2018 Oct 25. PMID: 30358427. doi:** 10.1080/00224499.2018.1531367.
55. Magoun HW. The Waking Brain. Springield, Ill: Charles C. Thomas; 1958.
56. Vance EB, Wagner NN. Written descriptions of orgasm: a study of sex differences. **Arch Sex Behav 1976;5:87–98 PMID: 1259556. doi:** 10.1007/BF01542242.
57. Komisaruk BR, Beyer-Flores C, Whipple B. The science of orgasm. Baltimore, MD: Johns Hopkins University Press+ ORM; 2006.
58. Hornby TG, Rymer WZ, Benz EN, et al. Windup of flexion reflexes in chronic human spinal cord injury: a marker for neuronal plateau potentials? **J Neurophysiol 2003;89:416–426 PMID: 12522190. doi:** 10.1152/jn.00979.2001.
59. Aby F, Bouali-Benazzouz R, Landry M, et al. Windup of nociceptive flexion reflex depends on synaptic and intrinsic properties of dorsal horn neurons in adult rats. **Int J Mol Sci 2019;20:6146. PMID: 31817540; PMCID: PMC6940907. doi:** 10.3390/ijms20246146.
60. Berić A, Light JK. Anorgasmia in anterior spinal cord syndrome. **J Neurol Neurosurg Psychiatry 1993;56:548–551 PMID: 8505649; PMCID: PMC1015017. doi:** 10.1136/jnnp.56.5.548.
61. Willis WD. The somatosensory system, with emphasis on structures important for pain. **Brain Res Rev 2007;55:297–313 Epub 2007 Jun 12. PMID: 17604109. doi:** 10.1016/j.brainresrev.2007.05.010.

62. Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). **Neurophysiol Clin 2000;30:263–288 PMID: 11126640. doi: 10.1016/s0987-7053(00)00227-6.**
63. Komisaruk BR, Whipple B, Crawford A, et al. Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the vagus nerves. **Brain Res 2004;1024:77–88 PMID: 15451368. doi: 10.1016/j.brainres.2004.07.029.**
64. Wise NJ, Frangos E, Komisaruk BR. Brain Activity Unique to Orgasm in Women: An fMRI Analysis. **J Sex Med 2017;14:1380–1391 Epub 2017 Oct 3. PMID: 28986148; PMCID: PMC5675825. doi: 10.1016/j.jsxm.2017.08.014.**
65. Steinman JL, Komisaruk BR, Yaksh TL, et al. Spinal cord monoamines modulate the antinociceptive effects of vaginal stimulation in rats. **Pain 1983;16:155–166 PMID: 6877846. doi: 10.1016/0304-3959(83)90205-1.**
66. Whipple B, Ogden G, Komisaruk BR. Physiological correlates of imagery-induced orgasm in women. **Arch Sex Behav 1992;21:121–133 PMID: 1580785. doi: 10.1007/BF01542589.**
67. Schmidt-Wilcke T, Fuchs E, Funke K, et al. GABA-from inhibition to cognition: emerging concepts. **Neuroscientist 2018;24:501–515 Epub 2017 Oct 12. PMID: 29283020. doi: 10.1177/1073858417734530.**
68. Mills-Finnerty C, Frangos E, Allen K, et al. Functional magnetic resonance imaging studies in sexual medicine: a primer. **J Sex Med 2022;19:1073–1089 Epub 2022 Apr 11. PMID: 35422400; PMCID: PMC9246958. doi: 10.1016/j.jsxm.2022.03.217.**
69. Komisaruk BR, Whipple B. Non-genital orgasms. **Sexual and Relationship Therapy 2011;26:356–372.**
70. American Psychiatric Association. Diagnostic and statistical manual of mental disorders DSM 4 TR (text revision). Arlington, VA: American Psychiatric Association; 2003.
71. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, Fifth edition. Arlington, VA: American Psychiatric Association; 2013. p. 433–437.
72. Scheaffer H. Female Orgasmic Disorder DSM-5 302.73 (F52.31). Therapedia. 2022. Available at: https://www.therapedia.com/therapedia/female-orgasmic-disorder-dsm-5-302.73-(f52.31)
73. IsHak WW, Tobia G. DSM-5 changes in diagnostic criteria of sexual dysfunctions. **Reprod Sys Sex Disord 2013;2. doi: 10.4172/2161-038X.1000122.**
74. Perelman MA. Why the sexual tipping point model? **Curr Sex Health Rep 2016;8:39–46.**
75. Perelman MA. Why the Sexual Tipping Point is a "variable switch model". **Curr Sex Health Rep 2018;10:38–43.**
76. Pfaus JG. Pathways of sexual desire. **J Sex Med 2009;6:1506–1533 Epub 2009 Apr 30. PMID: 19453889. doi: 10.1111/j.1743-6109.2009.01309.x.**
77. Meston CM, Bradford A. Sexual dysfunctions in women. **Annu Rev Clin Psychol 2007;3:233–256.**
78. Goldstein I. Orgasmic Anhedonia (PDOD). Available at: https://www.sandiegosexualmedicine.com/female-issues/orgasmic-anhedonia-pdod. Accessed August 24, 2022.
79. Ho N, Sommers M. Anhedonia: a concept analysis. **Arch Psychiatr Nurs 2013;27:121–129 Epub 2013 Apr 24. PMID: 23706888; PMCID: PMC3664836. doi: 10.1016/j.apnu.2013.02.001.**
80. Kalmbach DA, Ciesla JA, Janata JW, et al. Specificity of anhedonic depression and anxious arousal with sexual problems among sexually healthy young adults. **J Sex Med 2012;9:505–513 Epub 2011 Oct 24. PMID: 22024317. doi: 10.1111/j.1743-6109.2011.02533.x.**
81. Schaub AC, Kirschner M, Schweinfurth N, et al. neuronal mapping of anhedonia across psychiatric diagnoses: A trans-diagnostic neuroimaging analysis. **Neuroimage Clin 2021;32:102825 Epub 2021 Sep 16. PMID: 34544030; PMCID: PMC8455863. doi: 10.1016/j.nicl.2021.102825.**
82. Keedwell PA, Andrew C, Williams SC, et al. The neuronal correlates of anhedonia in major depressive disorder. **Biol Psychiatry 2005;58:843–853 Epub 2005 Jul 25. PMID: 16043128. doi: 10.1016/j.biopsych.2005.05.019.**
83. Zhu H, Wang W, Sha C, et al. Pharmacological Characterization of Toludesvenlafaxine as a Triple Reuptake Inhibitor. **Front Pharmacol 2021;12:741794 PMID: 34594228; PMCID: PMC8476831. doi: 10.3389/fphar.2021.741794.**
84. Cao B, Zhu J, Zuckerman H, et al. Pharmacological interventions targeting anhedonia in patients with major depressive disorder: a systematic review. **Prog Neuropsychopharmacol Biol Psychiatry 2019;92:109–117 Epub 2019 Jan 3. PMID: 30611836. doi: 10.1016/j.pnpbp.2019.01.002.**
85. Argyropoulos SV, Nutt DJ. Anhedonia revisited: is there a role for dopamine-targeting drugs for depression? **J Psychopharmacol 2013;27:869–877 Epub 2013 Jul 31. PMID: 23904408. doi: 10.1177/0269881113494104.**
86. Gorwood P. Neurobiological mechanisms of anhedonia. **Dialogues Clin Neurosci 2008;10:291–299 PMID: 18979942; PMCID: PMC3181880. doi: 10.31887/DCNS.2008.10.3/pgorwood.**
87. Jacobsen PL, Mahableshwarkar AR, Chen Y, et al. Effect of Vortioxetine vs. Escitalopram on Sexual Functioning in Adults with Well-Treated Major Depressive Disorder Experiencing SSRI-Induced Sexual Dysfunction. **J Sex Med 2015;12:2036–2048 Epub 2015 Aug 31. PMID: 26331383. doi: 10.1111/jsm.12980.**
88. Martin-Tuite P, Shindel AW. Management options for premature ejaculation and delayed ejaculation in men. **Sex Med Rev 2020;8:473–485 Epub 2019 Oct 23. PMID: 31668585. doi: 10.1016/j.sxmr.2019.09.002.**
89. Leiblum S. Persistent genital arousal disorder: what it is and what it isn't. **Contemp Sex 2006;40:8–13.**
90. Komisaruk BR, Lee HJ. Prevalence of sacral spinal (Tarlov) cysts in persistent genital arousal disorder. **J Sex Med 2012;9:2047–2056 Epub 2012 May 17. PMID: 22594432. doi: 10.1111/j.1743-6109.2012.02765.x.**