Understanding sexual arousal and subjective—genital arousal desynchrony in women

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Abstract | Sexual arousal in women comprises two components: genital arousal and subjective arousal. Genital arousal is characterized by genital vasocongestion and other physiological changes that occur in response to sexual stimuli, whereas subjective arousal refers to mental engagement during sexual activity. For some women, genital arousal enhances subjective arousal; for others, the two types of arousal are desynchronous. However, the relationship between genital and subjective arousal might not be relevant to the diagnosis and treatment of sexual arousal dysfunction. Studies have shown that not all women who report sexual arousal problems have decreased genital arousal, and only some women with decreased genital arousal have low subjective arousal. To develop efficacious treatments for female sexual arousal dysfunction, researchers need to differentiate the women for whom genital sensations have a critical role in their subjective arousal from those who are not mentally aroused by genital cues. The mechanisms by which women become aroused and the inputs into arousal have considerable implications for treatment outcomes.

Since the introduction of sildenafil (Viagra; Pfizer) to the market in 1998 and the enormous success it proved in treating male arousal problems in the form of erectile dysfunction (ED), a great deal of research has been devoted to developing a vasoactive drug that might similarly enhance sexual arousal in women. Two decades later, such a drug has not yet been approved by the FDA, the European Medicines Agency, Health Canada, or Australia's Therapeutic Goods Administration. However, the flurry of pharmaceutical research devoted to the cause has undoubtedly led to a greater understanding of women's sexual arousal. Although many questions about how best to conceptualize sexual arousal in women remain unanswered, the two components to sexual arousal in women, genital arousal and subjective arousal, are generally well accepted^{1,2}. Genital sexual arousal refers to the physiological, genital changes that occur in response to sexual stimuli, including genital vasocongestion, vaginal lubrication, and clitoral engorgement, and is associated with other physiological, extragenital changes, including increased heart rate, sweating, pupil dilation, hardening and erection of the nipples, and flushing of the skin. Subjective sexual arousal (also referred to as 'mental sexual arousal', 'cognitive sexual arousal', and feeling 'turned on') might be best described as positive mental engagement and focus in response to sexual stimuli³ (FIG. 1).

Most theorists discuss women's sexual arousal in terms of a feedback mechanism between these two components, but some studies indicate that genital and subjective sexual arousal are not closely connected for some women⁴. Increases in genital arousal tend to occur somewhat automatically, within seconds of the onset of an erotic stimulus, and can occur even in the absence of subjective reports of feeling sexually aroused⁵. Moreover, the degree of connectivity between genital and subjective arousal seems to be unrelated to sexual arousal function and dysfunction in women. This disconnection raises the question of what exactly sexual arousal in women is and whether physiological changes that occur in the absence of a subjective sexual experience should even be considered a sexual response. In this Review, we provide an overview of the aetiology and measurement of genital and subjective sexual arousal in women and provide an in-depth discussion of the relationship between components of arousal in women from both a clinical and a theoretical perspective.

Aetiology of genital arousal

Vaginal lubrication is the first observable sign of genital arousal in women⁶. Basal vaginal fluid, also referred to as vaginal transudate, is produced from a variety of glands and epithelia, including the abdominal peritoneal cavity, the fallopian tubes, the uterus, the cervix,

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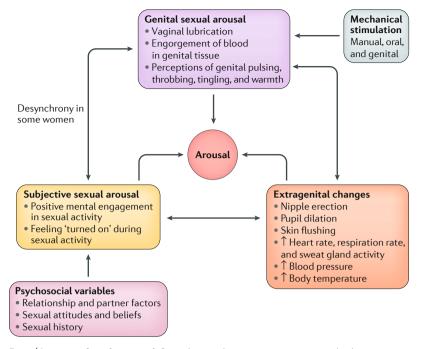


Fig. 1 | **Inputs to female arousal.** Sexual arousal in women comprises multiple interrelated components. Genital changes include vaginal lubrication and blood engorgement in the genital tissue. Extragenital changes include nipple erection, pupil dilation, and skin flushing. Subjective arousal is characterized by positive mental engagement during sexual activity.

the vaginal wall, and the Bartholin's glands, which are located on both sides of the entrance to the vagina7. This fluid does not fully lubricate the vagina; rather, the basal fluid makes vaginal surfaces moist enough to prevent adhesions but not wet enough to prevent pain during penetration⁷. Vaginal and labial lubrication are needed to facilitate painless intercourse. As arousal increases, vasocongestion in the tissues and increased capillary pressure force more fluid into the tissues, which increases the volume of fluid to the surface of the vaginal epithelium7. Oestrogen receptors expressed on the vaginal epithelium and in the smooth muscle cells of the muscularis have an important role in the production and maintenance of vaginal lubrication, as they are responsible for ensuring adequate lubrication and thickness of the vaginal wall, preserving the integrity and health of vaginal tissue, and influencing nerve transmission. By regulating cellular processes within the tissue of the vagina, oestrogen facilitates the growth and optimal function of neurons, blood vessels, smooth muscle, and cells within both the endothelium and the epithelium⁸. Improvement in the structure and thickness of the vaginal epithelium likely mediates improvements in genital blood flow, as fuller tissue contains a higher density of capillary beds, which facilitates increased blood supply to the genitals and increased lubrication^{9,10}.

Fluctuations in the sodium–potassium balance of the vaginal tissue also mediate the production of vaginal lubrication¹¹. When women are not sexually aroused, vaginal fluid has relatively high potassium and low sodium concentrations^{11,12}. During sexual arousal, the movement of vaginal fluid between cells increases the capacity of the cells for sodium transfer¹². When the cells become saturated with sodium, they cannot be reabsorbed into the epithelium; instead, they gather on the vaginal surface, increasing the pH of the vaginal canal^{13,14}.

Androgens, including dehydroepiandrosterone (DHEA), can also facilitate increased lubrication via aromatization to oestrogens¹⁵. Indeed, treating ovariectomized rats with topical DHEA resulted in the reversal of vaginal tissue atrophy and stimulated vaginal lubrication¹⁶. DHEA and its DHEA sulfate account for 75–100% of endogenous oestrogens in women both before and after menopause^{17,18}. When circulating oestrogen decreases after menopause, vaginal lubrication also decreases, and reductions in local oestrogen levels after menopause result in the thinning of the vaginal epithelium and the atrophy of smooth muscle in the vaginal wall. This process ultimately decreases vasodilation, lubrication, and genital sensations¹⁹.

After ~20 seconds of sexual stimulation, the onset of vaginal lubrication is followed by an increase in vaginal vasocongestion to the internal and external genitalia²⁰. The vascular system of the vagina is a complex network. The vaginal artery, which is composed of numerous arteries on each side of the pelvis, is connected to both the anterior and the posterior vaginal surfaces. During the initial phase of arousal, precapillary arterial dilation gradually shifts to arterialized blood flow and increased venous output²¹. Blood flow into the vaginal and genital region leads to engorgement and swelling of tissue in the vestibule and venous plexus, which surround the lower portion of the vagina. As blood pools in these areas, the vaginal walls become dark purple. Vasocongestion results from increased heart stroke volume and from the relaxation of smooth muscle cells in the walls of arteries that supply genital tissue, causing vasodilation²². Muscle relaxation enables the lengthening and dilation of the vagina, the protrusion of the clitoris, and the engorgement of the vestibular bulbs¹⁹. The clitoris retracts under the clitoral hood, and uterine elevation also occurs, probably caused by the contraction of parametrial muscle fibres that surround the vagina and uterus²³. When the tissues in the outer third of the vagina have fully expanded, complete vaginal vasocongestion has occurred⁶. Throughout this process, well oxygenated blood is supplied to the skin and breasts²⁴, contributing to extragenital sensations in the breasts, nipples, and inner thighs. Through this vasodilation process, sildenafil and other phosphodiesterase 5 (PDE5) inhibitors have been shown to increase blood supply to the genitals in women; however, these drugs have not led to significant increases in women's overall subjective experience of arousal²⁵⁻²⁷.

Neurovascular mechanisms

Increased blood volume can be elicited by sensory innervation and subsequently central nervous system (CNS) activation. Mechanical stimulation (manual, oral, and genital) is an important source of input for genital arousal. A set of peripheral nerves links the genitals to the CNS. The pudendal nerve conveys sensory stimuli from the external genitals to the spinal cord and innervates the pelvic striated muscles²⁸. Specifically, when low-threshold pudendal sensory fibres are stimulated,

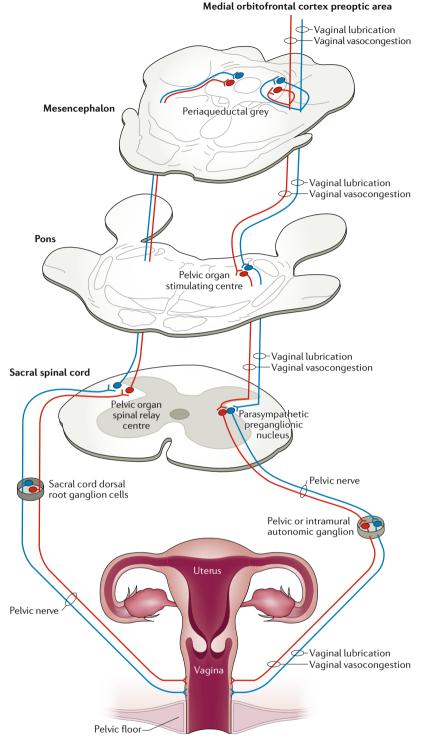


Fig. 2 | **Neural inputs to the female genitals.** The neural pathway involved in vaginal lubrication differs from the neural pathway that facilitates vaginal vasocongestion. Both pathways pass through the pelvic organ stimulating centre, the location of the inferior hypogastric plexus, where nerves project to the genital region. Figure reproduced with permission from REF.³⁰, Elsevier.

pudendal motor neurons are activated, leading to perineal muscle contractions²⁹. Other peripheral nerves, including the pelvic, hypogastric, and vagal nerves, contain both afferent and efferent fibres and contribute to the regulation of the genital response.

Both the parasympathetic and the sympathetic branches of the autonomic nervous system also facilitate vaginal vasocongestion. The pelvic organs are innervated by the sacral parasympathetic motor neurons, which are controlled by a specific group of neurons in the pelvic organ stimulating centre (POSC), an area of the pontine brainstem³⁰ (FIG. 2). The POSC activates the specific sacral parasympathetic motor neurons that are involved in generating vasocongestion and lubrication³⁰. Diffuse sympathetic nervous system (SNS) discharge occurs during the later stages of sexual arousal³¹, which precedes the increases in heart rate and blood pressure that occur during orgasm³². Increases in plasma noradrenaline, a marker of SNS activity, have been associated with increases in genital arousal during sexual activity³³. Research into sexual function in women who have suffered spinal cord injury (SCI) also provides strong support for the involvement of both the SNS and the parasympathetic nervous system (PNS). Women with SCI between segments T11 and L2 — the area of the spinal cord where the hypogastric sympathetic nerves project to the genital region - respond to erotic stimuli with a lack of lubrication³⁴. The union of hypogastric nerves and splanchnic fibres, which connects with the PNS between segments S2 and S4 (REF.³⁵), forms the inferior hypogastric plexus. This plexus innervates the cervix, upper vagina, urethra, vestibular bulbs, and clitoris. At the cervix, sympathetic and parasympathetic nerves join to form the paracervical ganglia³⁵. Mechanical stimulation by friction and pressure activates sensory nerves with cell bodies within the paracervical ganglia³⁶, generating nerve impulses to the spinal cord and probably to the vagus nerve³⁷, which facilitates parasympathetic control of the heart and other organs.

The relationship between the SNS and genital arousal has been investigated using exercise paradigms in the laboratory. In the first of these studies³⁸, women were asked to complete 20 minutes of intense exercise (designed to elicit SNS dominance) before viewing a film sequence composed of both neutral and erotic content (FIG. 3). The team compared the participants' genital arousal after exercise with their genital arousal during a no-exercise control session. Genital arousal was significantly higher during the post-exercise erotic film versus the control session. Importantly, no differences in genital responses were noted between sessions during the neutral film, indicating that exercise did not simply increase blood flow to the genitals; rather, it prepared the vagina for sexual arousal so that the body responded more efficiently when in a sexual context. The facilitatory effects of SNS activation on women's genital arousal have also been demonstrated using ephedrine to increase SNS activity³⁹, and SNS inhibition via clonidine has been shown to inhibit genital arousal in women⁴⁰. A 2012 study suggested that an optimal level of SNS activation results in the facilitation of sexual arousal in women⁴¹ such that moderate (versus very low or very high) increases in SNS activity are most beneficial for increasing genital arousal. Furthermore, the relationship between heart rate variability (HRV), a noninvasive index of relative balance of the two branches of the autonomic nervous system⁴², and sexual arousal in women also indicates the strength

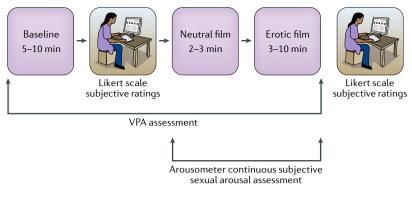


Fig. 3 | **Typical experimental paradigm in sexual psychophysiology research.** When women come to the laboratory, they insert the vaginal plethysmograph and complete a set of baseline questionnaires that assess affect and subjective arousal. They then watch a short neutral film, usually composed of nature scenes, followed by a short erotic film. While watching both films, women move the arousometer up or down to reflect changes in their subjective arousal. Finally, women complete a second set of questionnaires to measure changes in affect and subjective arousal and then they remove the plethysmograph. VPA, vaginal pulse amplitude.

of the association between the SNS and genital arousal⁴¹. Low resting state HRV is a risk factor for sexual arousal problems in women⁴³. Experimentally increasing HRV increases genital arousal in women without sexual dysfunction⁴⁴ and subjective sexual arousal in women with and without arousal concerns⁴⁵.

Hormonal mechanisms

Sex steroid hormones (oestradiol and testosterone) probably modulate genital blood flow by regulating the activity of vasoactive intestinal polypeptide (VIP) and nitric oxide synthase (NOS) in the vagina⁴⁶⁻⁴⁹. Vaginal tissue has a dense supply of VIP and NOS immunoreactive fibres that seem to be regulated by oestrogens and androgens⁵⁰. Originating in the ovaries, adipose tissue, and breasts, oestradiol modulates the expression and activity of neural and endothelial NOS, which then mediates the neurogenic relaxation response of both vaginal and clitoral smooth muscle⁵¹. Palle and colleagues⁴⁹ demonstrated the influence of oestrogen on VIP function by administering VIP to menopausal women who were either receiving or not receiving hormone replacement therapy (HRT). VIP only increased vaginal blood flow in women who were on HRT. Testosterone in the ovaries and the adrenals is also responsible for regulating NOS while also enhancing VIP-induced relaxation of the smooth muscle in the vagina⁵².

Prolactin and oxytocin indirectly affect genital sexual arousal and potentially subjective sexual arousal. Following masturbation-induced orgasm, serum prolactin levels increase significantly⁵³, which might act as a negative feedback signal limiting sexual arousal and decreasing the likelihood of continued sexual activity⁵⁴. Like prolactin, oxytocin seems to be more related to orgasm function than to genital arousal⁵⁵. However, oxytocin administration affects the orgasmic–postorgasmic interval and aspects of partner interactions, for example, contentment after intercourse⁵⁶. Although these effects are not specific to genital arousal, they might contribute to a positive feedback loop that facilitates both genital and subjective arousal with a particular partner (FIG. 4).

Aetiology of subjective arousal

Importantly, one must acknowledge that subjective arousal is a report about an experience — the experience of feeling mentally turned on. Evidence suggests that the anterior insular cortex provides the basis for all subjective feelings⁵⁷, contributing to emotional awareness and affecting subjective sexual arousal downstream. Subjective arousal requires attention to erotic cues and a generally positive appraisal of those cues. When a woman is exposed to a sexual stimulus, her genital response is largely automatic; however, her subjective response depends on her level of attention to the erotic stimulus and to other arousing cues, such as her partner's excitement and her own genital sensations⁵⁸. Experimental studies have provided evidence for a strong effect of attention on subjective arousal by demonstrating that distraction inhibits the sexual arousal response⁵⁹⁻⁶². According to Barlow's model of sexual dysfunction63, a continued focus on sexual cues increases subjective arousal and positive affect, whereas an attentional shift to internal cues or to critical, self-evaluative thoughts leads to negative affect and decreases sexual arousal. In addition to attention, other cognitive mechanisms, such as altered cognitive appraisal, can facilitate or hinder subjective arousal. The processes of appraisal give a stimulus event emotional meaning and shape both physiological and behavioural responses to the event⁶⁴. Thus, the appraisal of a sexual cue is important in determining whether a sexual response, including subjective sexual arousal, will occur⁵⁸. Women who appraise a sexual cue positively will be more likely to maintain their attention to that cue.

The degree to which women are able to mentally engage in sexual activity, positively appraise a stimulus as sexual, and experience subjective arousal is influenced by a number of psychosocial variables that can distract women from erotic cues. These include variables specific to the relationship and/or the partner, beliefs and attitudes about sexuality, and a history of sexual abuse and/or other negative sexual experiences. Although most of the studies that established these relationships did not explicitly differentiate between subjective and genital arousal, the assessment tools that were used — that is, self-report instruments — indicate that the authors were specifically focused on subjective arousal.

Relationship and partner factors

Women who are generally satisfied with the quality of their intimate relationships and those who report high levels of emotional intimacy with their partners are less likely to experience decreased arousal^{65,66}. Relationship factors can affect sexual arousal function if the woman is unable to communicate her sexual preferences to her partner. Specific sexual acts might not be mentally stimulating or pleasurable to the woman, or her partner might have limited sexual knowledge or skills. When partners communicate their sexual preferences and are responsive to sexual requests, they help mitigate problems with arousal and other types of sexual dysfunction^{67,68}.

Sexual problems in the male partner, particularly ED and premature ejaculation, can negatively affect a woman's sexual arousal. Successful treatment of

Sexual self-schemas

Cognitive generalizations about the sexual self that influence beliefs about sexuality and sexual behaviour. erectile problems can result in increased sexual arousal in the female partner, as well as improvements in other domains of sexual function^{69–71}. Indeed, one study showed that pharmacotherapy for ED was associated with improved sexual arousal, desire, and satisfaction among female partners⁶⁹. When interpreting their results, the authors of the study concluded that ED is a shared sexual dysfunction and that the sexual functions of men and women are interdependent in the context of the couple. Improving erectile function in the male partners might have also led to increased intimacy and emotional closeness between partners, which facilitate healthy sexual function in women⁷².

Beliefs and attitudes

Women who internalize negative attitudes towards sexuality or towards themselves might be at increased risk of experiencing low subjective arousal. Internalized guilt and shame related to certain sexual activities or to sexual expression in general have particularly potent effects on subjective arousal⁷³. Guilt associated with sexual experiences or sexual feelings has deleterious effects on sexual desire and arousal, even after religiosity is accounted for^{74,75}. Similarly, negative views about the sexual self and negative expectations about sexual encounters have been associated with decreased subjective arousal in the laboratory⁷⁶.

History of negative sexual experiences

A history of sexual abuse or of negative sexual experiences affects the beliefs and attitudes that women have towards sexual activity, and these beliefs can drive persistently low subjective sexual arousal⁷⁷. Many, but not all, women with a history of childhood sexual abuse avoid intimate sexual interactions and are less receptive to or turned on by sexual approaches from their partners⁷⁸. Sexual abuse at any developmental stage, but particularly if it occurs after menarche but before one's first consensual sexual experience, increases sexual embarrassment and conservatism⁷⁹ and might, therefore, affect a woman's ability to form sexually satisfying partnerships.

Sexual self-schemas, defined as cognitive generalizations about sexual aspects of the self that guide sexual behaviour and influence the processing of sexually

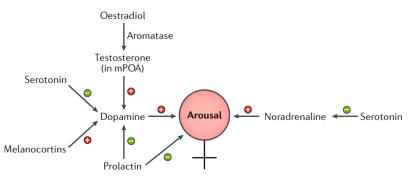


Fig. 4 | **Hormonal determinants of female arousal.** Several different hormones contribute to female sexual arousal, including the sex steroids (oestradiol and testosterone), dopamine, prolactin, and noradrenaline. mPOA, medial preoptic area. Figure adapted with permission from REF.¹⁶⁷, Elsevier.

relevant information⁸⁰, differ between women with and without a history of childhood sexual abuse^{81,82}. Women with negative sexual self-schemas or who have persistently negative associations with sexual activity might draw on those associations during sex, increasing distraction, preventing positive mental engagement, and, therefore, decreasing subjective sexual arousal⁶³.

Mood, anxiety, and perceived stress

Negative affect can have wide-ranging effects on female sexual function, and depressed mood can adversely affect subjective arousal. Decreased sexual arousal was reported by 40-50% of women with major depressive disorder⁸³. These women were not taking antidepressant medications, which are well-known to inhibit sexual arousal^{84,85}. Although the mechanisms underlying antidepressant-induced sexual dysfunction are not fully understood, serotonin is likely to be implicated⁸⁶. Selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin, which tends to diminish sexual function, whereas dopamine tends to enhance sexual function; thus, drugs that enhance serotonin or block dopamine are commonly associated with decreases in sexual arousal⁸⁷. The cognitive model of depression⁸⁸ suggests that women experiencing depressive symptoms are more likely to engage in negative self-talk, which is associated with lower arousal in both sexes73.

Anxiety related to sexual function or that occurs during sexual activity also negatively affects subjective sexual arousal. Women with sexual problems have higher rates of anxiety than sexually healthy women⁸⁹, and women with anxiety disorders are more likely to have sexual arousal dysfunction^{90,91}. Among sexually functional women, acute stress has been associated with decreased subjective sexual arousal⁹². Whether this association is due to cognitive mechanisms (such as distraction from sexual cues) or the result of changes in levels of certain neurotransmitters (for example, increased cortisol) is unclear; both cognitive and biological factors are likely driving the effect.

Concern over one's sexual performance (performance anxiety) can direct attention from sexual to nonsexual cues, ultimately leading to sexual distress and decreased subjective sexual arousal⁹³. Performance concerns in women are often directed at body image and/or perceived sexual attractiveness. In women, body image self-consciousness has been related to lower sexual esteem, less sexual assertiveness, greater sexual avoidance, and a lower probability of being in a relationship⁹⁴. Indeed, negative thoughts about one's physical appearance⁹⁵ or perceptions that a partner disapproves of one's body⁶⁶ can fuel anxiety and cognitive distraction during a sexual situation, as can fears of pregnancy and/or sexually transmitted infections^{96,97}.

Measuring arousal Measurement of genital sexual arousal

In 1968, Shapiro and colleagues⁹⁸ published the first promising method for measuring sexual arousal in women. This report came almost a quarter of a century after the first published measurement of male arousal⁹⁹. The technique described by Shapiro and

a Vaginal photoplethysmograph

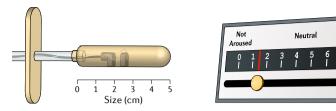


Fig. 5 | **Tools for measuring arousal. a** | The vaginal photoplethysmograph contains a photosensitive light detector and either an incandescent light source or an infrared diode. When inserted into the vagina, the light source illuminates the capillary bed of the vaginal wall. The amount of light that is reflected back into the device serves as an indirect index of vasocongestion. **b** | The lever for continuous measurement of subjective sexual arousal enables women to report their level of mental engagement while watching a sexual film.

co-workers98 consisted of two vaginal thermistors mounted on a cervical diaphragm (FIG. 5a). One of the thermistors was heated slightly by current flow in order to maintain a constant differential in temperature between the two thermistors. Differences between the thermistor-assessed temperature of the vaginal wall and core body temperature corresponded to the degree of capillary engorgement of the vagina. Before this method of measuring genital blood flow, researchers focused almost exclusively on extragenital measures of arousal, such as heart rate, respiration rate, blood pressure and body temperature changes, and sweat gland activity¹⁰⁰. Although these extragenital measures change with sexual arousal in women, they lack specificity, as they also change in response to anxiety, fear, excitement, and other affect-laden situations. Like Shapiro and colleagues' early measurement device, current techniques for assessing genital sexual arousal in women also rely primarily on indirect assessments of vaginal blood. The three primary means of assessing vaginal blood flow include vaginal photoplethysmography, indirect measures of heat dissipation, and pulsed-wave Doppler ultrasonography.

b Lever for continuous measurement

Verv

Aroused

The vaginal photoplethysmograph. The measurement of genital arousal in a laboratory setting most commonly involves a vaginal photoplethysmograph¹⁰¹ (FIG. 5b). Designed by Sintchak and Geer in 1975 (REF.¹⁰¹) and subsequently improved upon by Hoon and colleagues¹⁰², the vaginal photoplethysmograph is an acrylic, tampon-shaped device that contains either an incandescent light source or an infrared diode and a photosensitive light detector. The light source illuminates the capillary bed of the vaginal wall, and the phototransistor detects light that is reflected back into the device. The amount of back-scattered light directly relates to the transparency of engorged and unengorged vaginal tissue and, therefore, serves as an indirect index of vasocongestion. The method assumes that as the back-scattering signal increases, so too does the amount of blood in the vaginal wall²⁴. Two components of the signal can be derived from the photoplethysmograph: vaginal blood volume (VBV), thought to reflect slow changes to the pooling of blood in vaginal tissue, and vaginal pulse amplitude (VPA), which reflects phasic changes in vaginal engorgement with each heartbeat¹⁰³. VPA is

the measure most often reported in current studies and is thought to be superior to VBV in terms of sensitivity and construct validity^{38,103-106}. Advantages of using this device include the ability of subjects to insert the probe in privacy, without the assistance of a researcher, the ability to measure blood volume changes over somewhat long periods of time without harm or discomfort to the subject, and the somewhat short period of time required for VBV and VPA levels to return to baseline, enabling multiple, sequential assessments. Disadvantages include the sensitivity of the probe to movement artefacts, which precludes the measurement of changes in blood volume during orgasm, and the lack of a sound theoretical basis for interpreting where exactly the vasodilation is occurring.

Thermography. Thermography is a means of measuring physiological changes by detecting and photographing individual infrared patterns¹⁰⁷. This technique has been used to measure genital sexual arousal. Human skin and membranes constantly emit infrared radiation and other electrochemical energies. Over a short period of time, thermographic technology can detect these energies and produce thermal images from which the average temperature of <1 mm² of skin can be determined at a precision of 0.07 °C (REF.¹⁰⁸). Early studies that used this technique to measure sexual arousal documented genital temperature increases in both men and women that were specific to sexual situations¹⁰⁹⁻¹¹¹. Compared with VPA, changes in genital temperature peak more slowly during the presentation of an erotic stimulus¹¹². Thermography is noninvasive, it provides continuous, real-time assessment of anatomy and blood flow, and it can be used in both men and women, which facilitates comparison. Disadvantages include the high price of the equipment, a slow response to initial increases in arousal and a somewhat long period of time to return to baseline, a ceiling effect (that is, temperature cannot increase beyond the normal physiological range), poor temporal variability (a linear increase in genital temperature will positively correlate with any other variable that increases from baseline levels), and the need for an examiner in close proximity to the participant to monitor the equipment, which compromises participant privacy¹¹³.

Pulsed-wave Doppler ultrasonography. Doppler ultrasonography has been used to measure blood velocity in the clitoral cavernosal artery and to record changes in intravaginal pressure associated with changes in blood flow¹¹⁴. This technique uses ultrasound technology to produce an image of blood vessels and surrounding organs in real time. The Doppler sound waves from the image are converted into a graph, which highlights the speed and the direction of blood flow in the vessel that is being examined. The main advantages of this measurement technique include the ability to monitor during high levels of sexual arousal (owing to the relative absence of movement artefacts), the ability to record blood volume in absolute units (cm per second), and the ability to continuously assess both the anatomical and the vasocongestive components of the female sexual response. Disadvantages include the expense of instruments and the requirement for placement and continuous monitoring by a trained technician, both of which can adversely affect a woman's sense of comfort and privacy.

Measurement of subjective sexual arousal

Self-report questionnaires. Subjective sexual arousal is most commonly measured using a Likert-style, self-report questionnaire that asks a woman to report her level of mental arousal or feeling turned on. The standard laboratory protocol is to present a series of short videos — a nonsexual film (for example, a travel film or nature documentary) followed by an erotic film - and have the woman retrospectively report on her subjective arousal after the end of the erotic film. The benefits of this approach are ease of use and interpretation: participants simply rate their subjective arousal by answering a few short questions, and the data are typically averaged, which produces mean scores that are easily analysed¹¹⁵. Disadvantages include the use of retrospective assessment, which might capture a participant's poststimulus level of arousal rather than her arousal during the film. Furthermore, as the self-report questionnaire is typically given at only one time point, researchers cannot assess changes in subjective arousal alongside continuous measures of genital arousal, making it more challenging to examine the relationship between these two constructs. Discrete measures of subjective arousal are also susceptible to the social desirability bias¹¹⁶, which increases the tendency to respond in an unrealistically desirable way117.

Continuous measurement. Continuous measurements allow women to indicate their level of subjective sexual arousal throughout the presentation of an erotic stimulus in the laboratory. First created by Wincze and colleagues in 1977 (REF.¹¹⁸), continuous measurement devices generally consist of a lever or computer mouse mounted to a track¹¹⁹ that participants can effortlessly move with one hand during the erotic film stimulus to reflect changes in their subjective arousal. Women are instructed to move the device in a given direction when they feel mentally turned on and in the opposite direction when they feel turned off. Continuous measurement devices circumvent retrospective recall issues and enable subjective and genital sexual arousal to be assessed concurrently across time. Unlike discrete measures, continuous measures of subjective arousal have not been associated with the social desirability bias¹¹⁶. However, some researchers have speculated that continuously documenting one's subjective arousal during an erotic film could distract participants from focusing on erotic cues and potentially reduce their sexual arousal. To date, no data are available to support this speculation.

Assessing both aspects of arousal

Social desirability bias

The tendency of survey respondents to answer questions in a manner that will be viewed favourably by others. Several self-report measures include both genital and subjective arousal items to assess sexual arousal dysfunction. The Female Sexual Function Index (FSFI)¹²⁰, a 19-item, multidimensional instrument that assesses 6 components of female sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain), has 2 subscales that are relevant to arousal: the arousal subscale items measure subjective arousal (for example, "How would you rate your level of sexual arousal (turned on) during sexual activity or intercourse?"), and the lubrication subscale items assess genital wetness, a key aspect of genital arousal (for example, "Over the past 4 weeks, how often did you maintain your lubrication (wetness) until completion of sexual activity or intercourse?"). The Sexual Interest and Desire Inventory-Female (SIDI-F)¹²¹ is a brief, clinician-administered instrument that was developed to assess symptoms of hypoactive sexual desire disorder. The measure includes several arousal items (for example, "Over the past month, when you had sex, how often did you become aroused (sexually excited, wet, lubricated, etc.)?" and "Over the past month, when you had sex, how easily did you become aroused (sexually excited, wet, lubricated, etc.) in response to sexual stimulation?"). Although these items do not separate the genital component of arousal from the subjective component, they do assess both components of arousal. The Sexual Function Questionnaire (SFQ)122 has two genital arousal subscales, one that assesses genital sensations (warmth, pulsating, and tingling) and one that assesses lubrication. The SFQ also includes a sexual enjoyment subscale; although its items do not directly assess mental engagement during sex, they do provide some insight into the overall subjective experience of arousal.

Diagnosing arousal dysfunction

The relevance of subjective sexual arousal to conceptualizations of sexual arousal dysfunction has caused a great deal of controversy. In some editions, the Diagnostic and Statistical Manual of Mental Disorders references both subjective arousal and genital arousal in the diagnostic criteria for sexual arousal dysfunction^{123,124}; in others, the criteria focus exclusively on genital arousal¹²⁵⁻¹²⁷. The privileging of genital arousal over subjective arousal might be due, at least in part, to ongoing confusion surrounding the definition of the construct and from the longstanding use of the term subjective to describe women's mental sexual arousal. The Oxford English Dictionary definition of subjective is "based on or influenced by personal feelings, tastes, or opinions..."128, and, as such, pairing the term subjective with arousal indirectly implies that subjective arousal is unreliable or that a woman's mental experience of arousal is based on opinion rather than fact. Genital arousal is conceptualized as the objective, unbiased, and perhaps most important measure of sexual arousal in women, whereas subjective arousal is confused with desire and is, therefore, often left unaddressed¹²⁹. Subjective arousal has also been used to describe women's perceptions of their genital changes, which is a separate construct that we believe should be termed 'perceived genital sensations'. When some researchers define subjective arousal as positive mental engagement with a sexual stimulus and others use the term to indicate one's perception of her genital response, communicating about these constructs between research laboratories and with patients becomes complicated. Ultimately, failure to acknowledge the role of subjective arousal in the sexual experiences of women and failure to maintain a consistent definition of subjective arousal limits our understanding of female sexual arousal and sexual arousal dysfunction.

Relationship between genital and subjective arousal *Theoretical models*

Several theoretical models of arousal in women describe or acknowledge the relationship between genital and subjective arousal in different ways (FIG. 6). According to Basson's cyclical model¹³⁰ of the female sexual response, women's sexual function is motivated by both the biological urge to experience arousal and various nonsexual outcomes, such as emotional closeness, acceptance, and affection (FIG. 6a). Basson developed this model in response to concerns that genital responses and traditional indicators of sexual desire, such as fantasy and motivation to masturbate, were overshadowing other critical facilitators of sexual arousal and satisfaction in women, such as trust, intimacy, and communication. Arguing that these nonsexual rewards are often more motivating than the biological drive towards arousal and orgasm, Basson described the complex associations between subjective arousal, genital arousal, and perceived genital sensations, stating, "women's sexual arousal is a subjective mental excitement that may or may not be accompanied by awareness of vasocongestive changes in her genitalia and other physical nongenital manifestations of arousal. If there is genital awareness, it may or may not be an erotic stimulus to the woman"130. This model acknowledges the two components of sexual arousal in women while recognizing that mental excitement and genital changes might not be concurrent. That is, mental appreciation for the sexual stimulus, as well the experience of nonsexual rewards, can occur with and without objective genital changes and/or an awareness of those changes. Indeed, Basson and others have suggested that women are motivated to engage in sexual activity for a range of reasons beyond physiological arousal and orgasm. As many as 237 reasons for engaging in sexual intercourse have been documented¹³¹. The nonsexual reasons include stress reduction, mate guarding, insecurity, and a desire to increase intimacy.

Barlow's theoretical model63 of sexual dysfunction addresses the relationship between genital and subjective arousal less directly (FIG. 6b). Barlow purports that the locus and quality of the individual's attention during sexual activity and, relatedly, the degree of one's cognitive distraction are maintaining factors of sexual problems. During sexual activity, individuals with sexual dysfunction show a decreased focus on erotic and genital cues and an increased focus on nonerotic cues. These nonerotic cues can include maladaptive, negative thoughts about one's level of physical attractiveness or about one's performance during sexual activity. When such thoughts occur, positive mental engagement with the sexual stimulus decreases, creating a negative feedback loop in which increased arousal becomes associated with the psychological consequences of not performing, fuelling avoidance and negative expectancies of genital changes. Within this framework, subjective and genital arousal are distinct but intimately related - when negative thoughts override mental excitement, genital cues that might otherwise be interpreted as sexual and/or positive instead become cause for avoidance.

Janssen and Bancroft's¹³² dual control model proposes that sexual arousal and its associated behaviours depend on the balance between sexual excitation and inhibition (FIG. 6c). Taking individual variability into account, the model indicates that the weighing of excitatory and inhibitory processes determines whether or not sexual activity occurs within a specific situation. Although the authors do not explicitly distinguish subjective sexual arousal from the genital arousal response, we can infer that the interaction of these constructs can affect the activation or suppression of a sexual response. Within the framework of this model, both genital arousal and subjective arousal can act as excitatory and inhibitory forces, leading to sexual activity, sexual risk taking, and possibly sexual dysfunction.

The incentive motivation model put forth by Toates¹³³ suggests that sexual arousal emerges in response to a set of incentives or cues, and that each individual has a predisposition to sexual responsiveness that is influenced by both biological and psychological factors (FIG. 6d). According to the model, sexual behaviour exerts positive feedback by enhancing motivation and increases negative feedback through orgasm and ejaculation, which induce satiety and ultimately strengthen the power of future incentives. As this occurs, information processing also takes place. The autonomic genital reactions must be attended to and appraised as sexual⁵⁸, a process that can be both implicit and explicit. The implicit pathway (the unconscious detection of a sexual stimulus) can trigger genital changes, whereas the explicit pathway assumes a conscious application of a sexual meaning to a stimulus, which we suggest can trigger subjective arousal. Within this model, information on the consequences of genital reactions and changes (one consequence, among many, is the presence or absence of subjective arousal) feeds back to affect future sexual motivation.

Concordance

Traditionally, the level of concordance between genital and subjective arousal has been assessed through correlations. Continuous genital arousal data are collapsed or averaged and compared with subjective arousal, which is measured via a self-report, Likert-style scale. Laboratory studies that have examined concordance in women have consistently found low correlations (r = 0.26)⁴. In men, the same analyses produce strikingly higher correlations (r = 0.66), suggesting that genital arousal in men corresponds far more closely to subjective feelings of arousal than it does in women⁴. This discrepancy has garnered much attention, but although the gender difference is certainly of theoretical interest, it might not be clinically relevant.

Several explanations have been proposed to account for this gender difference. Low correlations between subjective and genital measures of arousal in women might be the result of negative affect that is induced when male-produced erotica is used as sexual stimuli. If man-made films are not associated with negative mood states among men, then these films could be responsible for the gender difference. Several studies have experimentally manipulated the type of erotic stimuli (female-centred versus male-centred) to test

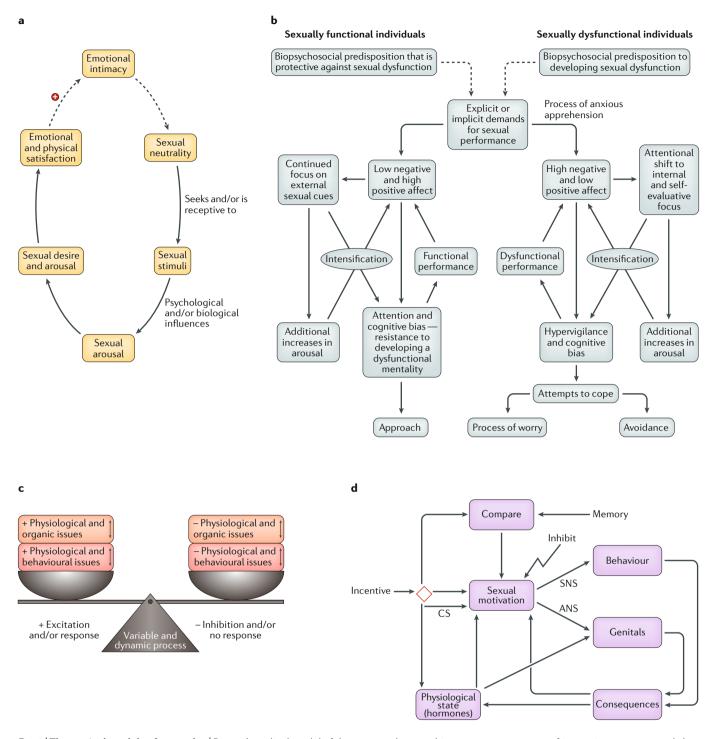


Fig. 6 | **Theoretical models of arousal. a** | Basson's cyclical model of the female sexual response cycle suggests that sexual desire and arousal are catalysed by both the biological urge to experience arousal and interest in various nonsexual outcomes, such as emotional closeness and intimacy. According to this model, sexual arousal in women is nonlinear. **b** | Barlow's model of sexual dysfunction indicates that the focus of one's individual attention and the degree of distraction during sexual activity are maintaining factors for sexual problems. Individuals with low arousal might focus on nonerotic cues rather than erotic or genital cues during sexual activity. **c** | Janssen and Bancroft's dual control model posits that sexual arousal and its related behaviours depend on the balance between sexual excitation and inhibition. The weighing of these two processes determines whether or not sexual activity occurs within a given context. **d** | Toates' incentive motivation model suggests that

sexual arousal is a response to a set of incentives or cues and that each individual's sexual responsiveness to these cues is determined by both biological and psychological factors. ANS, autonomic nervous system; CS, conditioned stimulus; SNS, sympathetic nervous system. Part **a** reproduced from REF.⁷², Human sex-response cycles, Basson, R., *Journal of Sex and Marital Therapy*, 2001, Taylor & Francis, reprinted by permission of the publisher (Taylor & Francis Ltd, http://www. tandfonline.com). Part **b** reproduced with permission from REF.¹⁶⁹, Indiana University Press. Part **c** adapted with permission from REF.¹⁶⁹, Elsevier. Part **d** adapted from REF.¹³³, An integrative theoretical framework for understanding sexual motivation, arousal, and behaviour, Toates, F., *The Journal of Sexual Research*, 2009, Taylor & Francis, reprinted by permission of the publisher (Taylor & Francis Ltd, http://www. tandfonline.com).

for differences in arousal; women tended to experience greater positive affect and subjective arousal with female-centred films than with male-centred films^{134,135}. However, results from a 2010 meta-analysis revealed that female-centred stimuli (films that were either produced by women or explicitly made for female audiences) did not increase the agreement between subjective and genital arousal in women⁴.

Anatomically, men have a more obvious arousal response than women. An erection is apparent and is, therefore, more easily acknowledged than vaginal vasocongestion. For this reason, men might find it easier than women to attend to their genital cues, providing a possible explanation for the observed gender difference in genital and subjective arousal. Although male attention to genital cues can be explained anatomically, their attendance to bodily changes might not be specific to sexual cues: men are also more accurate than women at detecting other physiological changes, such as differences in blood pressure, heart rate, and temperature¹³⁶. These observations do not necessarily suggest that women are incapable of attending to their genital cues; women do exhibit a significant degree of agreement between VPA and their subjective arousal when they are specifically directed to focus on their genitals. In one study, women who were told to monitor either their genital changes or their overall physiological changes had higher levels of concordance than women who were given no attentional cues137. A separate study in which women were asked to continuously rate their genital sensations during the presentation of the experimental films revealed that correlations between subjective and genital arousal were particularly high for women with greater interoceptive awareness¹³⁸. It is possible, then, that concordance levels for women who are more attentive to their internal cues might be similar to rates of concordance in men.

The fact that levels of concordance in the laboratory are higher in men than in women is theoretically intriguing but clinically irrelevant. The use of statistically sophisticated techniques that trace the agreement between genital and subjective arousal continuously throughout an erotic stimulus, such as hierarchical linear modelling (HLM), has enabled researchers to study response patterns over time. Unlike correlations, these sophisticated techniques do not obscure individual relationships, and they do not disguise nuances in the data. In a study of sexually functional women who showed significant increases in both genital and subjective sexual arousal to erotic films, results from HLM analyses showed wide variability between women in the degree to which genital arousal influenced their ratings of subjective arousal¹¹⁹. For some women, genital and subjective arousal were highly concordant; for others, no relationship was discernible whatsoever. Thus, genital sensations have an important role in their subjective experience of feeling turned on for some women, but for other women, factors such as contextual cues, relationship issues, body image, and past sexual history might be more meaningful in their subjective experience of sexual arousal than genital sensations.

Interoceptive awareness The perception of internal bodily sensations.

Some evidence suggests that concordance is related to sexual function, but a clear causal link between increased concordance and enhanced arousal has not yet been identified. In a meta-analysis by Chivers and colleagues⁴, the average sexual concordance correlation for women with diverse sexual difficulties was 0.04 (r = -0.10 to)0.17), compared with 0.26 in women without sexual concerns (r = 0.21 - 0.37). Several subsequent studies have examined the effects of interventions that are known to improve sexual arousal and have demonstrated that these treatments do increase concordance between genital and subjective arousal. These findings have led some researchers to suggest that concordance might be a key component to healthy sexual functioning in women¹³⁹. One such study concluded that a mindfulness-based treatment improved concordance among women with sexual desire and/or arousal difficulties¹³⁹. However, the strengthening of the relationship between genital and subjective arousal did not necessarily lead to meaningful decreases in symptoms or distress. A mindfulness intervention was also associated with increased subjective arousal and increased concordance in women without sexual dysfunction, but no explicit causal relationship was observed between increases in concordance and increases in sexual arousal¹⁴⁰. Other studies have demonstrated that sexual concordance is related to constructs relevant to sexual arousal and sexual function but did not show that increasing concordance directly facilitates improvements in sexual arousal^{140,141}. Indeed, Chivers and Brotto state that the notion that higher concordance is "a more valid expression of sexual response" is a misconception, which unfortunately drives the conclusion that, relative to the agreement between genital and subjective arousal in men, women's lower sexual concordance is deficient or problematic142.

Notably, research on arousal concordance comes from somewhat small data sets from few laboratories, and these data should be considered within that context. In the future, these data will need to be replicated in large, diverse samples that include participants of all ages with varied cultural, racial, and ethnic backgrounds.

Treating arousal disorders in women

Women who report decreased sexual arousal require individualized treatment strategies that can include a combination of biological, pharmacological, and behavioural approaches. Clinicians must match their treatment approaches to the specific presenting problems. In order to do so, they must conduct a thorough assessment that gauges both the intensity of specific sensations associated with genital arousal (such as warmth, pulsing, and tingling) and the level of mental engagement (that is, subjective arousal) during sexual activity¹⁴³. After clinicians have identified the main targets of treatment, they can direct their patients to the appropriate combination of interventions.

Biological treatments

Several hormonal treatments have been demonstrated to increase sexual desire and, in some cases, genital sexual arousal. In the USA, testosterone is often prescribed off-label in the form of patches or pills¹⁴⁴, as it has not yet been approved by the FDA or Health Canada to treat low sexual desire in women. Estrogen and tibolone therapy

are other hormonal options for sexual function problems related to vulvovaginal atrophy. Given the strong relationship between low levels of oestrogen and vaginal tissue atrophy, estrogen therapy is particularly effective for this concern¹⁴⁵. Tibolone, a 19-notestosterone derivative that regulates oestrogenic activity, is typically used to treat postmenopausal women with vaginal dryness¹⁴⁶. Women receiving tibolone have reported increases in lubrication, desire, and overall sexual function¹⁴⁷.

Nonhormonal, centrally acting medications have also been tested among women with low desire and arousal concerns. When used to treat hypoactive sexual desire among nondepressed women, bupropion (Wellbutrin), a noradrenaline-dopamine reuptake inhibitor, led to modest improvements in both sexual interest and arousal¹⁴⁸. Similarly, when buspirone (BuSpar), a serotonin 5-HT1, partial agonist, was administered to counteract the negative sexual adverse effects of an SSRI, the drug led to substantial improvements in sexual function compared with placebo. Several combination drugs are currently in development for the treatment of sexual desire and arousal concerns. Lybrido is the combination of sublingual testosterone and a PDE5 inhibitor¹⁴⁹; it was developed for women who have a low sensitivity to sexual cues, and it has been associated with significant increases in sexual satisfaction compared with placebo150,151. A separate drug called Lybridos combines sublingual testosterone and buspirone, which aims to counter sexual inhibition during sexual situations149. Like Lybrido, Lybridos has been associated with increases in sexual satisfaction among women with sexual dysfunction¹⁵².

The EROS clitoral therapy device, though not a pharmacological option, is the only FDA-approved treatment for arousal concerns in women. It is a small handheld device that specifically targets genital sexual arousal by increasing vasocongestion in the clitoris and the labia via a suction mechanism. Though the device is not widely used, it has been associated with increased vaginal lubrication and genital sensations¹⁵³.

Psychosocial treatments

Sensate focus, cognitive behavioural therapy, and mindfulness-based approaches are typically used by clinical psychologists and sexual medicine providers to increase sexual arousal in women.

Sensate focus encourages each partner in a couple to focus on bodily sensations derived from touch during sexual activity, taking turns being the 'giving partner' and the 'getting partner'¹⁵⁴. Over several sessions, a couple goes through a hierarchical series of touching, massaging, and fondling, beginning with nonverbal, nonsexual touch without full body contact or kissing, followed by the inclusion of sexual touch (genital areas and breasts), and eventually allowing for penile-vaginal insertion, if clinically appropriate¹⁵⁵. Studies using sensate focus suggest that it is effective for treating women with a variety of sexual concerns including low sexual arousal¹⁵⁶. Effectiveness for enhancing sexual arousal is likely attributable to a decrease in anxiety during sexual activity and an increase in the focus of attention to erotic cues and sensations.

Similar in many ways to sensate focus, mindfulness is a clinical technique that increases body awareness through the self-regulation of attention onto an immediate experience with "curiosity, openness, and acceptance"¹⁵⁷ and away from goal-centred results. Participants are taught to experience potentially distracting thoughts (for example, a focus on performance or appearance) as "passing events of the mind" and to refrain from reacting to them. Within the context of sexuality, mindfulness involves the awareness and acceptance of sexual sensations and feelings as they occur¹⁵⁸. Mindfulness-based approaches increase sexual desire and improve some arousal indices, but the arousal findings tend to vary by study¹⁵⁶. In the studies that measure genital arousal, mindfulness does not seem to have a significant effect^{159,160}, whereas the improvements seem to be more consistent with trending or significant increases in subjective arousal159-161 and significant increases in desire and perceived lubrication^{161,162}. The mechanisms driving the effect of mindfulness on female sexual function might occur via increased interoceptive awareness and attention to sexually relevant physiological cues^{163,164}.

Cognitive behavioural techniques can be used to challenge beliefs or thoughts that undermine sexual arousal, such as unrealistic expectations of performance, body image concerns, and other distracting or negative thoughts¹⁶⁵. Cognitive restructuring can increase subjective arousal by helping women identify their core fears (such as a fear of abandonment or rejection) and their maladaptive beliefs (for example, "My partner is not attracted to me") and then testing the accuracy of those beliefs through behavioural experiments. For example, a woman who will have sex only in the dark might feel that her partner would reject her or leave her if he saw her body in the light. She has likely amassed a series of negative associations about sexuality and sexual activity, which might compromise her ability to positively engage with sexual stimuli. A cognitive behavioural therapist would encourage her to incrementally increase the amount of light in the room to test the reaction of her partner and ultimately counteract her maladaptive beliefs, which would hopefully increase her mental sexual excitement during sexual activity. Only a few studies have tested cognitive behavioural therapy-based treatments for female sexual dysfunction, and none have focused specifically on female sexual arousal disorder. In a study that included women with a range of sexual problems, cognitive behavioural therapy was most likely to be effective for arousal and orgasm difficulties¹⁶⁶.

Conclusions

Sexual arousal in women is determined by physiological genital changes (vasocongestion and vaginal lubrication) and nongenital cues (increased heart rate, sweating, pupil dilation, and hardening and erection of the nipples) that occur in response to sexual stimuli and are modified by factors that affect the psychological experience of feeling subjectively aroused, such as relationship status and past sexual history. Addressing both genital arousal and subjective arousal is critical when conceptualizing sexual arousal concerns (FIG. 1). Unfortunately,

with some exceptions, including the FSFI¹²⁰, the SFQ¹²², and the SIDI-F¹²¹, existing psychometric tools are limited in that they do not assess both genital and subjective components.

The level of concordance between genital and subjective arousal has yet to be strongly related to improvements in women's sexual arousal function. However, this desynchrony between genital and subjective sexual arousal commonly seen in both sexually functional women and in women with arousal dysfunction is frequently misinterpreted as cause for clinical concern. As a consequence, much research has focused on developing treatments to improve concordance, such as mindfulness-based techniques to train women to attend to genital cues; however, from a clinical perspective, the only women who would benefit from increasing their attention to their genital sensations are those for whom genital sensations have a substantial role in their subjective experience of feeling sexually aroused. In a similar manner, drugs aimed at increasing blood flow to the genitals, such as sildenafil, can be expected to benefit only women who complain of a decrease in genital arousal sensations and place great significance on genital sensations in their experience of subjective arousal. For this reason, despite two decades of attempts to develop a vasoactive drug for treating sexual arousal dysfunction in women, an FDA-approved female counterpart to drugs for male arousal dysfunction is yet to be developed. The end goal of vasodilator PDE5 inhibitors — such as sildenafil, vardenafil, and tadalafil — is to increase blood flow into the genitals, but not all women who complain of sexual arousal dysfunction have decreased blood flow to the genitals, and not all women who have decreased blood flow to the genitals experience sexual arousal concerns.

In the future, researchers need to more carefully identify a target group of women who would best benefit from treatments that aim to increase genital vasocongestion — those who experience decreased genital arousal and who also incorporate genital arousal cues into their subjective arousal experience. Women who do not incorporate these cues will be more likely to benefit from treatments that address concerns about the relationship and/or the partner, maladaptive beliefs about sexuality, and previous negative sexual experiences than drugs that alter genital blood flow. The gender difference in synchrony between genital and subjective sexual arousal indicates that men, more so than women, readily incorporate genital sensations into their subjective experience of sexual arousal and emphasizes the fact that applying a male template to the development of treatments for women's sexual arousal concerns is theoretically and clinically inappropriate.

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Both authors researched data for the article, made substantial contributions to discussions of content, wrote the article, and reviewed and edited the manuscript before submission.

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