Review Article

The Reproductive Functions of the Human Brain Regions: A Systematic Review

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Abstract

Reproduction remains a vital characteristic of living things necessary for survival and continuity. Specific brain regions and structures are responsible for regulating the different aspects of human reproduction. This study systematically reviewed the brain regions that play structural, hormonal and physiological roles in controlling the various aspects of human reproduction from puberty, sexual function, gametogenesis, childbirth and fertility to infertility to inform advancement in research and therapeutic interventions in human reproductive disorders. A systematic literature search of online databases (MEDLINE, Europe PMC and Google Scholar) was made using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for observational and cross-sectional studies providing evidence for the role(s) of the brain region in human reproduction from the year 2011–2021. Out of 141 articles found, 15 studies met the inclusion criteria, including six cross-sectional and nine randomised controlled trials. The study acknowledged the roles of the pituitary gland, hypothalamus and pineal gland, widely known for regulating the human reproductive system in a gender-based approach while highlighting essential gaps and opportunities for future research. This review provides a 10-year update and overview of the role of different brain regions in human reproduction and will stimulate future research in human reproduction.

Keywords: *Brain function, female reproduction, fertility, human reproduction, male reproduction, neurophysiology, update review*

Introduction

Reproduction, a biological process that ensures the formation of new organisms, remains a crucial feature of living things necessary to preserve life and the continuity of species. In higher animals, including humans, reproduction mainly occurs sexually through mating.[1] While the goal of the reproductive system may be the same in males and females, there are remarkable variations in the anatomy and functional regulation in both sexes. In males, the reproductive system comprises the testes as the primary sex organ, playing both gametogenic and endocrine roles.[2] It also includes accessory organs such as the seminal vesicle, prostate gland, urethra and penis.[3] On the other hand, the female reproductive system consists of the ovaries as its primary sex organ. The ovaries produce eggs (ova) and secrete oestrogen and progesterone. The female reproductive system also includes the mammary glands and other accessory organs such as the fallopian tube, uterus, cervix, vagina, labia majora, labia minora and clitoris.[2]

One of the most critical factors of the reproductive system is its regulation for optimal function. The

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brain is the control centre of the human body and plays a huge role in regulating reproduction. The brain commands task-evoked responses, senses, movement, emotions, language, communication, thinking and memory.[4] Several brain regions such as the pituitary gland, hypothalamus and pineal gland are widely known for regulating the reproductive system. The hypothalamus is a small part of the diencephalon with endocrine functions. It receives many signals from various regions of the brain. It produces both releasing and inhibiting hormones that act on the pituitary gland to direct the functions of several endocrine glands and other structures of the body.[5] The pituitary gland (master endocrine gland) is divided into the anterior (adenohypophysis) and posterior (neurohypophysis) pituitary[6] and is connected to the hypothalamus through a tract of nerves – hypothalamo-hypophyseal tract – by some nuclei in the hypothalamus (paraventricular nucleus and supraoptic nucleus.[6] The hormones oxytocin and anti-diuretic hormone are secreted from the posterior pituitary under the influence of the hypothalamus. Hormones such as thyrotropin-releasing hormone, gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone (GHRH), corticotropin-releasing hormone, somatostatin and dopamine are released from the hypothalamus into the blood and travel to the anterior pituitary.[6]

The hypothalamus, pituitary gland and gonads (testes and ovaries) with feedback loops constitute the hypothalamic–pituitary–gonadal (HPG) axis.[7] The HPG axis is a very common link between the brain and the reproductive system. The secretion of GnRH by specialised hypothalamic neurons initiates the neuroendocrine activity of the axis. Once GnRH is delivered to the anterior pituitary (adenohypophysis), it stimulates the gonadotrophs to secrete luteinising hormone (LH) and follicle-stimulating hormone (FSH). These two hormones are collectively referred to as gonadotropins. They, in turn, stimulate sex steroid production and gametogenesis in the gonads.[8] In females, FSH and LH are responsible for regulating ovarian functions, and in males, LH is primarily responsible for stimulating specialised cells in the testes (Leydig cells) to produce testosterone. In contrast, FSH plays a significant role in regulating the seminiferous tubule and spermatogenesis via its action on the Sertoli cells.[9]

It has also been shown that the pineal gland and its hormone – melatonin – have physiological functions in the regulation and/or modulation of female reproductive activities: pregnancy and cessation of reproductive activity in middle age.[10] Beyond the familiar functional role of the brain in human reproduction, this study highlights some of the critical regions of the brain that play roles in regulating or affecting reproduction – from puberty, sexual function, gametogenesis, childbirth and fertility to infertility. These roles were analysed to provide an update and a gender-based perspective while highlighting essential gaps and opportunities for future research.

Materials and Methods

Study protocol

The study protocol of this systematic review has been registered on the OSF REGISTRIES, an open registries network, and can be accessed here: Https://osf.io/fbsw8/.

Search strategy

A systematic search strategy was utilised for this evidence synthesis. Searches were conducted using the electronic database [MEDLINE (via PubMed), Europe PMC and Google Scholar]. The search terms used were in accordance with Medical Subject Heading (MeSH) terms and have been documented in detail [Supplementary File 1]. Search duplications were removed after the database search. Manual searches were also conducted through snowballing using the reference lists from already identified articles. Searching ceased when data saturation was reached, and substantial information were available to answer the research question.

Study selection and data extraction

One hundred and forty-one articles were identified through database search (136 studies) and snowballing (five studies). However, only fifteen studies were included for qualitative synthesis after article screening based on the inclusion criteria [Figure 1]. Article search was limited to 10 years (January 2011 to May 2021) to conform with the study's aim of synthesising an update review. We considered only corresponding and observational studies published in the English language for inclusion in this review. However, case studies and review articles were not included in the articles reviewed in the current study. All animal-based studies were also excluded. Table 1 summarizes the findings of the included studies, whereas Figure 2 depicts the mapping of the brain roles in human reproduction. The authors retrieved the studies and extracted data independently to reduce the risk of bias. All areas of conflict were resolved after discussion or with an external expert.

Quality assessment of included studies

All the studies included in this review were assessed for quality using the National Institutes of Health (NIH)

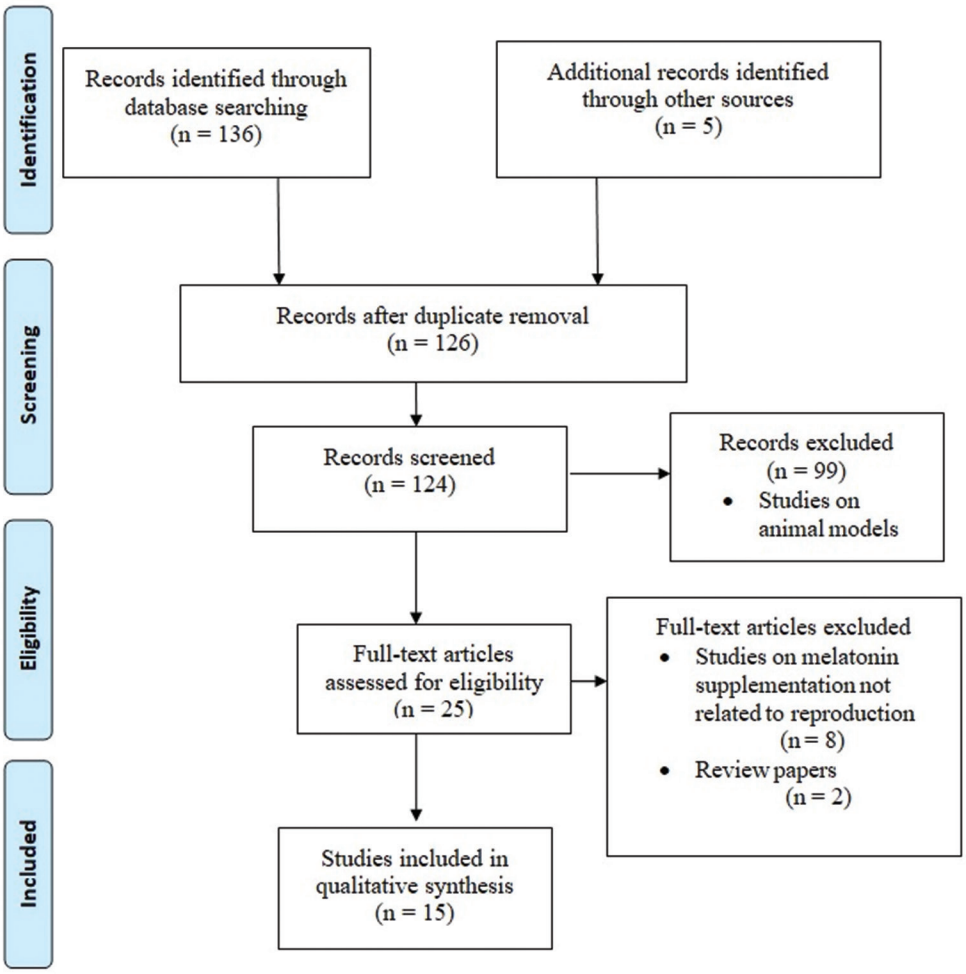

Figure 1: Schematic on literature search strategy

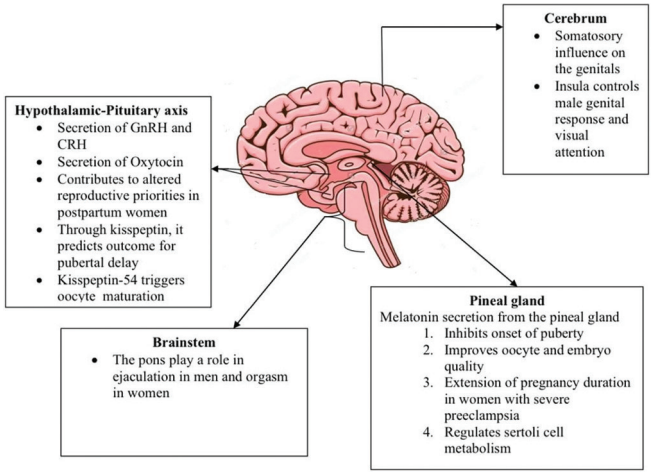

Figure 2: Mapping of different brain regions and their functions in human reproduction. GnRH: Gonadotropin-releasing hormone; CRH: Corticotropin-releasing hormone

assessment criteria.[11] Further, the randomised clinical trials (RCTs) were also assessed using the Jadad scoring quality assessment criteria[12,13] to give a comparative quality assessment of the included studies.

Results

Description of included reviews

Table 1 shows the summarised descriptions of the included studies and the effects different brain areas have on the male and female reproductive systems. This review included fifteen studies made up of 6 cross-sectional studies (40%) and 9 RCTs (60%). The studies were published between January 2011 and May 2021, with about 40% (6 articles) published within the past 5 years. Ten studies (66.67%) had only females as study participants, while only one study (6.67%) was done exclusively on males. However, four studies (26.67%) had a combination of males and females as participants. Six studies (40%) were on the pineal gland, five (33.33%) were on the HPG axis, one (6.67%) was on the pons and three (20%) were on the cerebrum. The included studies utilised different methods to assess the roles and effects of the various brain parts on the reproductive system. Five studies (33.33%) used neuronal stimulation, four (26.67%) used melatonin supplementation,

Table 1: Summary of main findings from the included studies

Author(s)	Study type	Sample size	Brain area implicated in the study	Methods	Summary of findings (male reproduction)	Summary of findings (female reproduction)
Komisaruk *et al*. 2011[15]	Cross-sectional	11 females	Cerebrum	Neuronal stimulation	NA	Somatotopy of the clitoris, vagina and cervix
Allen *et al*. 2020[14]	Cross-sectional	21 males	Cerebrum	Neuronal stimulation	Somatotopy of the urogenital system Nipple projection to the same somatosensory region as the genitals	NA
Cera *et al*. 2020[17]	RCT	19 males	Cerebrum	Neuronal stimulation	Insula controls male genital response and visual attention	NA
Eryilmaz *et al*. 2011[18]	RCT	60 females	Pineal body	Melatonin supplementation	NA	Improvement of oocyte and embryo quality in IVF patients with sleep disorder
Greendale *et al*. 2020[23]	Cross-sectional	20 females	Pineal body	Urine analysis	NA	secretion of melatonin is involved in cycle pacemaker control in menstruation
Espino *et al*. 2019 [20]	Cross-sectional	40 females	Pineal body	Melatonin supplementation	NA	Melatonin supplementation re-balanced the intrafollicular oxidative status in unexplained infertile patients with low melatonin levels
Rad *et al*. 2015[22]	Cross-sectional	60 females	Pineal body	Blood sampling	NA	Melatonin and its correlation with oxidative stress biomarkers, could be involved in infertility
Hobson *et al*. 2018[21]	RCT	20 females	Pineal body	Melatonin supplementation	NA	Melatonin mitigates maternal endothelial pro-oxidant injury
Batiioğlu *et al*. 2012[19]	RCT	85 females	Pineal body	Melatonin supplementation	NA	Low melatonin levels in infertile women result in poor oocyte and embryo quality Melatonin administration improves the oocyte and embryo quality in women undergoing IVF
Gregory *et al*. 2015[47]	RCT	59 females	HPG axis	Neuronal stimulation	NA	Oxytocin contributes to the altered reproductive priorities in post-partum women
George *et al*. 2011[24]	RCT	6 males	HPG axis	kisspeptin-10 administration	Kisspeptin stimulates GnRH and thus gonadotropin secretion Kisspeptin-10 evokes LH secretion in men, and continuous infusion increases testosterone, LH pulse frequency and pulse size	NA
Jayasena *et al*. 2013[25]	RCT	6 females	HPG axis	kisspeptin-54 administration	NA	Kisspeptin-54 temporarily stimulates the number of LH pulses in healthy women
Yee-Ming *et al*. 2020[27]	RCT	13 males; 3 females	HPG axis	kisspeptin and GnRH stimulation test	Kisspeptin is useful in predicting outcomes for individuals with pubertal delay	kisspeptin is useful in predicting outcomes for individuals with pubertal delay

Contd...

Table 1: Contd...

Author(s)	Study type	Sample size	Brain area implicated in the study	Methods	Summary of findings (male reproduction)	Summary of findings (female reproduction)
Abbara *et al*. 2015[26]	RCT	60 females	HPG axis	Kisspeptin administration	NA	Kisspeptin-54 triggers oocyte maturation in a cohort of women at high risk of OHSS
Huynh *et al*. 2013[16]	Cross-sectional		Pons	Neuronal 11 males; 11 females stimulation	Pontine regions in the brainstem activated during ejaculation	Pontine regions in the brainstem activated during orgasm

RCT=Randomised clinical trial, NA=Not applicable, GnRH=Gonadotropin-releasing hormone, LH=Luteinising hormone, IVF=*In vitro* fertilisation, HPG=Hypothalamic–pituitary–gonadal, OHSS=Ovarian hyperstimulation syndrome

three (20%) used kisspeptin administration, and one study each (6.67%) used urine analysis, blood sampling and kisspeptin and GnRH stimulation test.

The studies that employed neuronal stimulation on the cerebrum (three studies), pons (one study) and HPG axis (one study) reported findings such as the somatotopic stimulation of the nipples and genitals,[14] stimulation of the clitoris, vagina and cervix[15] and stimulation of ejaculation and orgasm.[16] The insula (part of the cerebrum) was involved in controlling male genital response and visual attention.[17] The studies on melatonin supplementation affecting the pineal gland (body) reported improvements in oocyte and embryo quality,[18,19] re-balancing of intrafollicular oxidative stress level in infertile participants[20] and the prevention of maternal endothelial pro-oxidant injury.[21] A low level of melatonin was correlated with oxidative stress biomarkers, which could be involved in infertility.[22] Furthermore, the optimal secretion of melatonin was found to be involved in the control of menstruation.[23] The studies on kisspeptin administration found that kisspeptin administration affected the HPG axis and resulted in the stimulation of GnRH and thus gonadotropin secretion,[24] evoking of LH secretion in men,[24] an increase in testosterone and LH pulse frequency and size,[24,25] triggering of oocyte maturation[26] and reversal of pubertal delay.[27]

Quality assessment of included studies

The NIH-NHLBI quality assessment criteria[11] were employed to assess the quality of all the studies recruited for this review. However, the RCTs alone were further graded using the Jadad scoring criteria to give a comparative quality assessment for the clinical trial. Following the NIH-NHLBI evaluation, 10 out of 15 studies (66.67%) were good studies, while others were fair. None of the included studies were poor based on the assessment. The Jadad scoring for quality assessment of the RCTs revealed that 5 out of 9 of the studies (55.55%) were rated high (having scores between 3 and 5), while others were low (scores < 3). The Jadad assessment of RCTs reduced the number of good studies that were included from six (following NIH-NHLBI criteria) to five studies [Supplementary Files 2-4].

Discussion

The synthesised evidence from the included studies showed that various portions of the human brain exerted critical structural, physiological and hormonal influences on the male and female reproductive systems.

The cerebrum

The cerebrum contains the largest and most developed information processing networks of the human brain.[28] It is located above the brainstem, consists of two hemispheres and has four lobes. Its outer grey-coloured surface (cerebral cortex) is responsible for the neuronal computations underlying complex phenomena, such as perception, thought, language, attention, episodic memory and voluntary movement.[29] The studies,[14,15,17] on the prospective roles of the cerebrum on the human reproductive system utilised neuronal stimulation of the cerebrum. Komisaruk *et al*.[15] mapped the female genitals in the sensory cortex using functional magnetic resonance imaging. They used the thumb and great toes stimulation as a reference point on the homunculus (a map along the cerebral cortex where each body part is located and their sensations processed). Their study revealed that clitoral, vaginal and cervical self-stimulation responses were found in the medial paracentral lobule (a U-shaped convolution situated on the medial side of the cerebral hemisphere), with the precise localisations being different from each other. The study coincidentally found that nipple self-stimulation in women, which was initially selected as a reference point on the homunculus, also activated the medial paracentral lobule. Their study is the first to report clitoral, vaginal and cervical self-stimulation localisation on the medial paracentral lobule rather than on some other location like the dorsolateral aspect. Komisaruk *et al*.[15] provide evidence that vaginal and cervical stimulation activated distinct regions of the sensory cortex different from

clitoral sensory stimulation. This knowledge is essential, especially in activating the diverse and differential consequences of clitoral, vaginal or cervical stimulation, including their differential physiological effects, for example, prolactin secretion[30] and analgesia[31] and other physiological functions. The only possible weakness of their study is the small sample size (11 females) used.

In their study, Allen *et al*.[14] successfully mapped sites on the primary somatosensory cortex to which components of the male reproductive system project. Their study found that nipple stimulation in men activated regions of the medial paracentral lobule, which could be why nipple stimulation is considered erotogenous. Evidence from their research showed that the location of the response to mild tactile stimulation of the penile glans or shaft was distinct from the site of the response to forceful squeezing of the glans or shaft. This was confirmed because mild tactile self-stimulation activated the paracentral lobule, which is consistent with the Penfield and Rasmussen male genital representation.[32] Furthermore, Allen *et al*.[14] characterised the neural differences between 'erotic' and 'prosaic' touch, which showed that top-down mental imagery and fantasy play a significant role in erotic arousal in men. The findings of their study provide helpful evidence on potential target sites for therapeutic interventions for sexual arousal disorders in men.

The pineal body

The pineal body, an endocrine gland located in the epithalamus, produces hormones with important regulatory influences on many endocrine organs, including the pituitary, thyroid, parathyroid, adrenals and gonads.[33] Its primary hormone, melatonin, possesses multifunctional biopotentials such as anti-oxidative, anti-inflammatory, anti-apoptotic, endocrinology and behavioural functions.[18] The studies involving the pineal body utilised various investigative methods such as melatonin supplementation[18-21] urine analysis[23] and blood sampling.[22]

In their study, Eryilmaz *et al*.[18] investigated the role of melatonin *in vitro* fertilisation-embryo transfer (IVF-ET) outcomes in patients with sleep disturbances. The study showed that IVF patients with sleep disorders might benefit from melatonin administration in improving the oocyte and the embryo quality, but the sleeping problem itself may not be resolved. Their study provides evidence that the pineal gland, through its melatonin production, has the potential to improve oocyte and embryo quality.

Greendale *et al*.[23] investigated the role of melatonin in the menstrual cycle, menopause and ageing. The study showed that higher circulating melatonin levels are more likely to be involved in menstrual cycle pacemaker control. This finding corroborates a previous study by Wetterberg[34] on the possible role of melatonin as a cycle pacemaker. They also found a 30% reduction in melatonin levels in postmenopausal collections, although it was not confirmed if the decline was due to ageing, menopause or both. Previous studies support the hypothesis of lower melatonin secretion with increasing age, but more studies of melatonin in ageing and menopause are recommended to elucidate the mechanisms and dynamics of these effects.[35-37]

In another study on the role of melatonin on female reproduction, Espino *et al*.,[20] showed that women with unexplained infertility had marked reduced concentrations of melatonin and oxidative imbalance in their follicular fluid, which may have influenced the poor quality of their oocytes and may be related to the low success rate of assisted reproductive technology. Melatonin has been shown to have a significant correlation with oxidative stress biomarkers in both fertile and infertile women, suggesting that melatonin levels could be involved in infertility.[22] Epsino *et al*.[20] found that melatonin supplementation re-balanced the intrafollicular oxidative status, improved oocyte quality and slightly enhanced IVF success rates in unexplained infertile patients. Although their study was devoid of blinding and had a small sample size (40 females), it agrees with another report[38] that have established a relationship between low melatonin levels and decreased antioxidant capacity, poor oocyte and embryo quality and a low fertilisation rate in the infertile women.

Hobson *et al*.[21] showed that melatonin mitigated maternal endothelial pro-oxidant injury. They found that melatonin reduced xanthine/xanthine oxidase-induced placental oxidative stress but not the production of anti-angiogenic factors. Melatonin in the study also mitigated TNFα-induced vascular cell adhesion molecule expression and rescued the subsequent disruption to endothelial monolayer integrity but did not affect other markers for endothelial activation and dysfunction. It is believed that melatonin mitigates TNFα-induced vascular cell adhesion molecules by protecting the endothelial adherens and tight junctional proteins, such as VE-cadherin, occludin, claudin-5 and ZO-1.[39-41] Their results indicate that melatonin could provide effective adjuvant therapy to extend pregnancy duration to deliver improved clinical outcomes for women with severe preeclampsia but not likely to be effective as either a preventative therapy or a placental repair therapy in preeclampsia as corroborated by other reports.[42] Information on randomisation and blinding of the study participants was not included in their study.

Soleimani Rad *et al*.[22] investigated the possible role of melatonin as a free radical scavenger. The result showed that melatonin levels are lower in infertile women than in those who are fertile. Total antioxidant capacity and malondialdehyde level in fertile women were found to be significantly higher when compared to infertile women. They concluded that melatonin as a scavenger of free radicals such as reactive oxygen species (ROS) could play a crucial role in enhancing and regulating reproduction in females. Their study agrees with a previous report[43] that established that melatonin as an antioxidant directly affects oocyte maturation and embryo development. It has been reported that excess amounts of ROS negatively affect human reproduction.[44] The study by Soleimani Rad *et al*.[22] has shed more light on the possible use of melatonin as an antioxidant in infertility treatment.

In their study, Batıoğlu *et al*.[19] evaluated the efficacy of melatonin administration on oocyte quality in women who underwent IVF cycles. The results showed that melatonin improved oocyte and embryo quality and fertilisation rates in women undergoing IVF. The study showed that melatonin could protect oocytes from the toxic effects of oxidative stress by being an excellent free radical scavenger. Their work agrees with other studies,[45,46] that have shown the positive influence of melatonin on oocyte and embryo quality and pregnancy outcome.

The hypothalamus–pituitary–gonadal axis

The studies on the roles of the HPG axis utilised kisspeptin administration,[24-26] kisspeptin stimulation test (Chan *et al.,* 2020, and neuronal stimulation.[47]

Kisspeptin, a neuropeptide, is known for its role in the HPG axis. Kisspeptin is produced by specific neurons in the hypothalamus and has stimulated GnRH and thus gonadotropin secretion.[24]

George *et al*.[24] hypothesised that kisspeptin-10, a minimal kisspeptin sequence with full intrinsic bioactivity, increased the secretion of GnRH in men. In their study, the administration of kisspeptin-10 boluses resulted in potent and dose-dependent stimulation of LH secretion in healthy men. Its continuous infusion increased testosterone, LH pulse frequency and pulse size. These findings align with a previous study on an animal model where intracerebroventricular doses of kisspeptin affected robust LH stimulation.[48] The stimulatory effects of kisspeptin-10 established in this study could inform future studies using kisspeptin as a diagnostic or therapeutic agent.[24]

Jayasen *et al*.[25] also investigated the stimulatory effects of kisspeptin on gonadotropin secretion using Kisspeptin-54 in a study done on six healthy females. They reported that a single subcutaneous injection of kisspeptin-54 increased the number and secretory mass of LH pulses in healthy female volunteers and could significantly impact the use of kisspeptin in restoring LH pulsatility in women with reproductive disorders.

Chan *et al*.[27] investigated the ability of kisspeptin to predict outcomes for individuals with pubertal delay in a cohort of 3 girls and 13 boys presenting with delayed or stalled puberty who were followed longitudinally. Kisspeptin secreted in the hypothalamus is known to stimulate GnRH secretion in humans and other animals.[49] The kisspeptin-stimulation test accurately predicted the participants' pubertal outcomes, and the results were more reliable than other tests for evaluating delayed puberty. The study discovered that the kisspeptin stimulation test provided the first method to measure a child's future potential for GnRH secretion. Kisspeptin was reported to elicit LH responses in children who eventually progressed through puberty when they appeared prepubertal on physical examination and daytime laboratory evaluation. One stated limitation of the study is the small sample size used. A large-scale assessment of the kisspeptin stimulation test will be needed for a more accurate assessment of the sensitivity and specificity of the test for predicting pubertal outcomes.

IVF treatment, though beneficial, can result in ovarian hyperstimulation syndrome (OHSS).[50] The use of kisspeptin-54 to trigger oocyte maturation in a cohort of women at high risk of OHSS was studied by Abbara *et al*.[26] Their results showed high rates of oocyte maturation, high implantation rates and no cases of clinically significant OHSS. Although using a GnRH agonist to trigger ovulation has become the most widely used strategy to prevent OHSS, recent case reports still show that it does not eliminate the occurrence of severe OHSS in high-risk populations.[50] An ideal trigger for inducing oocyte maturation in patients undergoing IVF treatment would yield high oocyte maturation rates, allow for high implantation rates, and, more importantly, a low risk of inducing OHSS.[51] The result from Abbara *et al*.[26] holds up great hope since kisspeptin stimulated GnRH in IVF patients, resulting in high rates of oocyte maturation with no case of OHSS. More extensive clinical studies are recommended to substantiate their findings.

The pons

The brainstem, consisting of the midbrain, the pons, and the medulla, connects the cerebrum to the spinal cord and cerebellum. It is responsible for many vital life functions, such as breathing, consciousness, blood pressure, heart rate and sleep.[52]

Huynh *et al*.[16] identified regions in the brainstem activated during ejaculation and female orgasm. In humans, a region in the dorsolateral pontine tegmentum on the left side and another in the ventrolateral tegmentum on the right side of the brain were activated during ejaculation in men or orgasm in women. The activation pattern was much stronger in men than women, which may be due to the weaker, shorter-lasting and less consistent motor component of orgasm in women than the motor component of male ejaculation.[53,54] The activation in the ventrolateral pontine tegmentum was explicitly induced by ejaculation in men or physical orgasm in women and not by associated sexual stimuli, nor was it induced in women who attempted but failed to reach orgasm or who initiated orgasm during the period of the scan by making voluntary movements of the pelvis. In the male, ejaculation is the endpoint that often results in the seminal fluid passing through the urethra into the vagina. Like micturition, it is dependent on supraspinal influences to coordinate the characteristic actions of activity in the pelvic organs. Bilateral lesion to the PMC located in the rostral pons results in urine retention.[55] However, the terminations of the PMC neurons on all parasympathetic motor neurons in the sacral cord suggest that the PMC is also involved in controlling pelvic floor organs engaged in functions other than micturition. The report on this study shows that this control may extend to the muscular contractions associated with ejaculation; as such Huynh *et al*.[16] deemed the term PMC inappropriate and suggested that a more accurate terminology should be the pelvic organ-stimulating centre (POSC). They observed that the pons was laterally activated during ejaculation or orgasm in men and women. Activation was detected in the POSC only on the left side of the brain.[16] The opposite activation pattern was observed during micturition when activation of the POSC was present only on the right side.[56] There is evidence for lateralised localisation in the forebrain processing of emotion.[57] While ejaculation and micturition are essentially voiding activities, the former is arguably associated with a much higher level of emotional arousal. It could explain why the POSC on the left side was only activated during ejaculation or orgasm. This study helps understand the complex processes involved in human sexual behaviour and could be a breakthrough in treating sexual disorders.

Limitation of the study

This review is a systematic 10-year update of the evidence on the roles of the human brain on human reproduction with consideration of articles published in English. The database searched for this present study was limited. Hence, the study may not represent all the available evidence and may not highlight previous pieces of evidence in detail. Furthermore, the quality of evidence used for this study seems suboptimal. None of the cross-sectional studies included in this review blinded the outcome assessors while most of the papers failed to justify the sample size (4 out of 6 articles) and only two articles reported the rate of eligible participants to be at least 50% while others did not report at all. Furthermore, only 1 out of 9 RCTs included in this study had a sample size that can detect a difference in the primary outcome between groups at a power of at least 80%. Seven articles did not report this at all. In general, there is a need to revalidate most of the synthesised evidence presented by the included studies using RCTs with a large sample size. Howbeit, the included studies demonstrate a little beyond preliminary evidence on the reported outcomes.

Future considerations

We have documented an update on the available evidence on the role of the brain in human reproduction. This presents many things to consider as future directions in terms of research. Sexual disorders such as low libido, ejaculation dysfunction and orgasmic disorders could be targeted by a streamlined focus on drug-target research on the POSC or the medial paracentral lobules of the cortex. When incorporated into the supplementation of oxytocin and/or melatonin, this target could open up new prospects for infertility, especially for ROS-related and unexplained infertility. As a result, more studies on the role of melatonin in the male reproductive system are recommended. It is essential to carry out RCTs with optimal sample size and effect size to achieve a more dependable outcome. This is also important for studies on Kisspeptin supplementation, which has shown great promise in successfully targeting infertility over the years to harmonise dosage, administration timing and modulated effects.

Conclusions

The brain is the body's most complex organ playing a vital role in regulating activities in all the systems of the body. Several brain parts have been implicated for their roles in the human reproductive process. These include the cerebral cortex, insula, pons, HPG axis and pineal gland. GnRH produced in the HPG axis stimulates the synthesis and release of FSH and LH from the anterior pituitary, regulating testicular and ovarian functions and stimulating oxytocin secretion responsible for uterine contraction during uterine contraction, childbirth and lactation. There is a somatosensory contribution in the sexual mapping of the genitals in the cerebral cortex, which makes it a prospective site for targeted therapy for sexual disorders. The pineal body, a subcortical

structure, is reported to improve oocyte and embryo quality and plays a role in the inhibition of puberty through melatonin secretion. The pons also plays a role in ejaculation in men and orgasm in women. Research on the part of the brain in human reproduction seems endless due to the complexity of the brain and the increasing impact of other factors such as genetics and environment on brain responses.

Availability of data

All the data generated have been included in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Files

Supplementary File 1

Article search databases and themes

Searches were conducted using the electronic database MEDLINE (via PubMed), Europe PMC, and Google Scholar. The following MESH terms and search terms were used: [brain] AND [reproduction], [cerebrum] AND [reproduction], [cerebral cortex] AND [reproduction], [insula] AND [reproduction], [cerebellum] AND [reproduction], [thalamus] AND [reproduction], [epithalamus] AND [reproduction], [pineal body] AND [reproduction], [melatonin] AND [reproduction], [hippocampus] AND [reproduction], [amygdala] AND [reproduction], [basal ganglia] and [reproduction], [caudate] AND [reproduction], [putamen] AND [reproduction], [globus pallidus] AND [reproduction], [brainstem] AND [reproduction], [midbrain] AND [reproduction], [pons] AND [reproduction], and [medulla] AND [reproduction].

Supplementary File 2: Quality assessment of randomised clinical trials using jadad scoring criteria

Author	1 Point if randomization is mentioned	1 Additional point if the method of randomisation is appropriate	1 Point if blinding is mentioned	1 Additional point if the method of blinding is mentioned	1 Point if there was a description of withdrawals and dropouts	Deduct 1 point if method of rando misation is inappropriate.	Deduct 1 point if the study was described as double blind but the method of blinding is inappropriate	Total	Grade
Cera *et al*. 2020[17]	1	1	0	0	0	0	0	2	Low
Eryilmaz *et al*. 2011[18]	1	1	0	0	1	0	0	3	High
Hobson *et al*. 2018[21]	0	0	0	0	1	0	0	1	Low
Batiioğlu *et al*. 2012[19]	1	1	1	1	0	0	0	4	High
Gregory *et al*. 2015[47]	1	1	1	1	1	0	0	5	High
George *et al*. 2011[24]	0	0	1	1	0	0	0	2	Low
Jayasena *et al*. 2013[25]	1	1	1	1	0	0	0	4	High
Yee-Ming *et al*. 2020[27]	0	0	0	0	1	0	0	1	Low
Abbara *et al*. 2015[26]	1	1	1	1	1	0	0	5	High

Supplementary File 3: Quality assessment of randomised clinical trials using National Institutes of Health-National Heart, Lungs and Blood Institute assessment criteria

Authors	Described as random	Adequate randomisation	Allocation concealment	Blinding btw participants and treatment group	Blinding btw people assessing the outcomes and participant's group	Similarity of group at baseline	Overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Differential drop-out rate (between treatment groups) at endpoint 15% points or lower
Cera *et al.* 2020[17]	Yes	Yes	Yes	No	No	Yes	NR	NR
Eryilmaz *et al.* 2011[18]	Yes	Yes	Yes	No	No	Yes	Yes	NA
Hobson *et al.* 2018[21]	No	No	No	No	No	Yes	Yes	Yes
Batiioğlu *et al.* 2012[19]	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR
Gregory *et al.* 2015[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
George *et al.* 2011[24]	No	No	No	Yes	NR	Yes	NR	NR
Jayasena *et al.* 2013[25]	Yes	Yes	Yes	Yes	No	Yes	NR	NR
Yee-Ming *et al.* 2020[27]	No	No	No	No	No	Yes	No	NR
Abbara *et al.* 2015[26]	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR

Authors	Adherence for each treatment group?	Avoidance of other interventions	Valid and reliable outcome measures assessment	Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power	Were outcomes reported or subgroups analysed pre-specified (i.e., identified before analyses were conducted)	Were all randomised participants analysed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis	Quality rating
Cera *et al.* 2020[17]	Yes	Yes	Yes	No	Yes	Yes	Good
Eryilmaz *et al.* 2011[18]	Yes	Yes	Yes	Yes	Yes	Yes	Good
Hobson *et al.* 2018[21]	Yes	Yes	Yes	NR	Yes	Yes	Fair
Batiioğlu *et al.* 2012[19]	Yes	Yes	Yes	NR	Yes	Yes	Good
Gregory *et al.* 2015[47]	Yes	Yes	Yes	NR	Yes	Yes	Good
George *et al.* 2011[24]	Yes	Yes	Yes	NR	Yes	Yes	Fair
Jayasena *et al.* 2013[25]	Yes	Yes	Yes	NR	Yes	Yes	Good
Yee-Ming *et al.* 2020[27]	Yes	Yes	Yes	NR	Yes	Yes	Fair
Abbara *et al.* 2015[26]	Yes	Yes	Yes	NR	Yes	Yes	Good

NR=Not reported, NA=Not applicable

Supplementary File 4: Quality assessment of cross-sectional studies using National Institutes of Health-National Heart, Lungs and Blood Institute assessment criteria assessment criteria

Author	Research question clearly stated	Study population clearly specified and defined	Rate of eligible participants at least 50%	Groups recruited from the same population and uniform eligibility criteria	Sample size justification	Exposure assessed prior to outcome measurement	Sufficient timeframe to see an effect	Different levels of the exposure of interest
Komisaruk *et al*. 2011[15]	Yes	Yes	NR	Yes	No	No	Yes	Yes
Allen *et al*. 2020[14]	Yes	Yes	NR	Yes	No	No	Yes	Yes
Greendale *et al*. 2020[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Espino *et al*. 2019[20]	Yes	Yes	NR	Yes	No	Yes	Yes	yes
Huynh *et al*. 2013[16]	Yes	Yes	NR	Yes	No	Yes	Yes	Yes
Rad *et al*. 2015[22]	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA

Author	Exposure measures and assessment	Repeated exposure assessment	Outcome measures	Blinding of outcome assessors	Loss to follow-up rate at baseline 20% or less	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)	Quality rating
Komisaruk *et al*. 2011[15]	Yes	Yes	Yes	No	Yes	Yes	Fair
Allen *et al*. 2020[14]	Yes	Yes	Yes	No	Yes	Yes	Fair
Greendale *et al*. 2020[23]	Yes	Yes	Yes	No	Yes	Yes	Good
Espino *et al*. 2019[20]	Yes	Yes	Yes	No	Yes	Yes	Good
Huynh *et al*. 2013[16]	Yes	Yes	Yes	No	Yes	Yes	Good
Rad *et al*. 2015[22]	Yes	No	Yes	NA	NA	Yes	Good

NR=Not reported, NA=Not applicable