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Review

Central neural mechanisms of lifelong premature ejaculation: a narrative synthesis of neuroimaging and electrophysiological evidence

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Abstract

Introduction: Premature ejaculation (PE) is one of the most prevalent male sexual disorders, with lifelong PE (LPE) affecting ~cx3%-5% of men. While peripheral, psychological, and relational factors are well-known contributing factors, accumulating neuroimaging and electrophysiological evidence suggests central neural mechanisms, including serotonergic, dopaminergic, and other neuromodulatory pathways play a role.
Objectives: To synthesize findings from neuroimaging and electrophysiological (electroencephalography) studies, providing an integrative perspective on the neural substrates of LPE and identifying gaps for future research.
Methods: A narrative review was conducted based on 43 original studies reporting structural-, functional-, and network-level neural correlates of LPE. The literature search and selection were performed in accordance with the Scale for the Assessment of Narrative Review Articles guidelines to ensure transparency and methodological rigor. Studies were categorized by modality, and findings were qualitatively synthesized to identify convergent patterns, regional alterations, and clinical correlations.
Results: Structural neuroimaging in LPE patients consistently demonstrates altered gray matter volume, cortical thickness, and white matter microstructure in prefrontal, orbitofrontal, striatal, thalamic, limbic, and temporal regions. Functional analyses reveal reduced top-down inhibitory control from prefrontal regions, hyperconnectivity within limbic–temporal sensory circuits, and dysregulated network dynamics across cortico-striato-thalamic pathways. Electroencephalography studies indicate abnormal cortical excitability and high-beta responses in frontal and temporal regions during sexual arousal. Multimodal studies show these neural alterations correlate with clinical severity, and machine learning models achieve high accuracy in differentiating LPE patients from healthy controls.
Conclusions: LPE is associated with distributed neural network dysfunction, characterized by impaired inhibitory control, exaggerated sensory processing, and dysregulation of serotonergic, dopaminergic, and other neuromodulatory systems. Although central changes may be both a cause and a consequence of LPE, these findings primarily advance mechanistic understanding and should be considered research-level indicators rather than diagnostic biomarkers.

Keywords: lifelong premature ejaculation; fMRI; DTI; Structural MRI; neural mechanisms.

Introduction

Premature ejaculation (PE) is among the most prevalent male sexual disorders, with an estimated lifelong prevalence of 3%-5%.[1,2] Although matter of future revision,[3] the lifelong PE (LPE) has been defined by the chronic inability to control ejaculation within about one minute of penetration and associated personal distress.[4] While peripheral, psychological, and relational factors have been discussed for decades, increasing evidence indicates that PE also involves central neural mechanisms.[5] The consistent efficacy of selective serotonin reuptake inhibitors (SSRIs) in prolonging ejaculation latency supports the view that central—and perhaps peripheral—serotonergic regulation of sexual response plays a crucial role.[6] However, the efficacy of SSRIs in treating PE does not account, as frequently but erroneously assumed[7]—that patients with PE necessarily have a derangement of the serotonergic pathway. A similar example is seen in erectile dysfunction: although phosphodiesterase 5 (PDE5) inhibitors are effective, their efficacy does not demonstrate that erectile dysfunction (ED) is caused by a pathological alteration in PDE5 activity or production.[8] Thus, other mechanisms should be examined.

Over the past decade, advances in neuroimaging (eg, functional magnetic resonance imaging: fMRI, diffusion tensor imaging: DTI) and electrophysiological (eg, electroencephalography: EEG) methods have provided unprecedented insights into the neural basis of ejaculatory control. These approaches enable in vivo assessment of brain activity, structural connectivity, and network organization, revealing how alterations in cortical and subcortical circuits might underline and/or mirror impaired inhibitory control and heightened sexual excitability observed in LPE.

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The available guidelines and the revisions of the current literature have broadly summarized the epidemiology, pathophysiological mechanisms, and management of PE.[9] However, most of these works only briefly touch upon neurobiological mechanisms, without systematically integrating evidence from functional and structural imaging, electrophysiology, and molecular imaging (positron emission tomography: PET). To date, no focused narrative review has synthesized the neuroimaging and electrophysiological evidence that specifically addresses the central neural involvement in LPE.

Therefore, the present review aims to fill this gap by providing an updated synthesis of 43 original neuroimaging and electrophysiological studies investigating brain structure, function, and connectivity in LPE. We summarize convergent and divergent findings across modalities, highlight emerging neurobiological models of ejaculatory control, and discuss methodological limitations and directions for future research. By integrating multimodal evidence, this review offers a novel perspective on the central involvement in LPE and their implications for diagnosis and treatment development.

Literature search and scope of the review

This narrative review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles guidelines,[10] ensuring transparency in literature search, selection, and synthesis. To ensure comprehensive coverage, a structured search was conducted in Google Scholar for studies published from 2008—when the International Society of Sexual Medicine (ISSM) definition of lifelong and acquired PE was introduced—through October 2025. The literature search was conducted using combinations of keywords based on the following search formula: ("premature ejaculation" OR "rapid ejaculation" OR "early ejaculation") AND (fMRI OR "functional MRI" OR "resting-state" OR "task fMRI" OR DTI OR "diffusion tensor" OR EEG OR "electroencephalography" OR PET OR "PET imaging" OR "positron emission" OR neuroimaging).

Eligible studies were included if they met the following criteria: (1) involved human participants diagnosed with LPE; (2) employed neuroimaging or electrophysiological techniques—including fMRI, MRI, DTI, PET, or EEG—to explore neural correlates of ejaculatory control; (3) reported outcomes related to brain structure, function, or electrophysiological activity associated with ejaculation regulation; and (4) were published in English-language, peer-reviewed journals.

Studies were excluded if they were review articles, animal experiments, case reports without neuroimaging or electrophysiological data, or focused solely on secondary PE or other sexual dysfunctions.

Following the application of these criteria, a total of 43 eligible studies were identified and subsequently categorized into two broad methodological groups. The first group comprised neuroimaging studies, which included findings from MRI, fMRI, and DTI. The second group encompassed electrophysiological studies, which incorporated evidence derived from EEG paradigm. It should be noted that an EEG-based study[11] was published in 2008, likely conducted before that year. Since the ISSM classification for LPE and APE was introduced in 2008, Hyun et al.'s study[11] did not use the ISSM definition of LPE. Nevertheless, we included it for the sake of completeness in this review.

Results and evidence synthesis

The 43 original studies included in our review are summarized in Table 1. Based on the synthesis of 43 original studies employing neuroimaging (fMRI, DTI, Structural Magnetic Resonance Imaging - sMRI) and EEG methods, we constructed a conceptual model summarizing the core neural pathways implicated in LPE (Figure 1).

Neuroimaging evidence

Over the past decade, neuroimaging studies have provided convergent evidence that LPE is associated with altered brain structure and function across regions involved in sensorimotor control, emotional regulation, and reward processing. fMRI, DTI, and structural MRI investigations consistently reveal dysregulation within the prefrontal–striatal–limbic–hypothalamic network, supporting the central origin hypothesis of LPE.

Functional connectivity and network reorganization

Resting-state fMRI studies have shown abnormal intrinsic connectivity in multiple networks governing inhibitory control and salience detection. LPE patients exhibit decreased functional connectivity (FC) between the striatum and insula, orbitofrontal cortex (OFC), superior temporal pole, and middle cingulate cortex, alongside increased FC between the caudate and OFC and between putamen and fusiform gyrus.[38] Similarly, hypothalamus-seeded FC analyses revealed reduced coupling with the insula, fusiform gyrus, parahippocampus, and cerebellum, suggesting compromised hypothalamic integration of limbic and autonomic signals.[39] These connectivity deficits correlated with intravaginal ejaculatory latency time (IELT), supporting their clinical relevance.

Dynamic functional connectivity analysis further demonstrated reconfiguration of temporal brain states in LPE. Patients spent more time in high-connectivity states with reinforced intra- and inter-network coupling, while transitions between network states were less flexible.[35] Such inflexibility may reflect maladaptive persistence of high-arousal neural states during sexual activity.

At the cortical level, hyperconnectivity in the middle temporal gyrus (MTG) and parahippocampal regions has been reported,[37] suggesting excessive engagement of perceptual–emotional circuits during sexual stimuli. Conversely, reduced FC in the default mode network and prefrontal control regions has been linked to impaired self-monitoring and ejaculatory inhibition.[19]

Structural and diffusion imaging findings

Structural MRI and DTI studies indicate microstructural reorganization in white matter tracts and gray matter morphology. Increased local efficiency and clustering coefficient were observed in the left inferior frontal gyrus and precentral gyrus, while—interestingly—divergent patterns in the left amygdala distinguished lifelong from acquired PE.[26] Source-based morphometry revealed gray matter volume abnormalities within the default mode and prefrontal networks, correlating spatially with neurotransmitter pathways including serotonin, dopamine, and γ-aminobutyric acid (GABA).[43]

In patients with comorbid depression, topological alterations in the striato-thalamo-cortical circuits were identified,

Table 1. Neuroimaging and electrophysiology studies of lifelong premature ejaculation.

Authors	Sample	Method	Task/condition	Key findings	Brain regions/metrics
Lu J, 2025[12]	28 LPE, 17 HCs	Resting-state fMRI, dynamic functional gradient	Task-modulated and task-free resting-state	Increased stability in bilateral dorsal PFC and right temporo-occipital-parietal cortex; correlated with sexual behavior	Bilateral dorsal PFC, right temporo-occipital-parietal cortex; functional gradient stability
Yang X, 2018[13]	38 LPE, 30 HCs	fMRI, FC analysis	Stop signal task	Abnormal correlation of SSRT with left IFG; weaker FC between left IFG and left dentate nucleus/right frontal pole	Left IFG, left dentate nucleus, right frontal pole
Bai Y, 2025[14]	26 LPE, 16 HCs	Task and resting-state fMRI, beta value, DC, FC	Glans penis electric stimulation	PE: higher beta in thalamus and IFG; rs-fMRI: increased DC in SMA, decreased DC in precuneus; enhanced FC IFG-SMA, decreased FC precuneus-thalamus	Bilateral thalamus, IFG, SMA, precuneus; beta value, DC, FC
Zhang B, 2017[15]	20 LPE, 15 HCs	Task and resting-state fMRI	Erotic picture stimuli, resting-state	Decreased activation in left IFG and insula; higher activation in right middle temporal gyrus; FC correlated with IELT/CIPE	Left IFG, left insula, right middle temporal gyrus, bilateral middle cingulate cortex, right middle frontal gyrus, SMA; FC
Kwon O Y, 2011[16]	5 LPE, 6 APE, 11 HCs	EEG, CSD	Erotic video, pre/post-sertraline	Increased CSD in superior frontal and right medial frontal gyrus post-sertraline	Superior frontal gyri, right medial frontal gyrus, middle/superior temporal, lingual/fusiform, inferior occipital, cuneus
Hyun J S, 2008[11]	18 PE, 18 HCs	EEG, LORETA	Resting, music video, erotic video	Decreased alpha-band CSD in PE patients; beta-2 and -3 bands decreased vs controls	Right precentral gyrus, right insula, superior parietal lobules, right parahippocampal gyrus, left middle temporal gyrus
Gao M, 2022[17]	23 drug-naive LPE, 30 HCs	Resting-state fMRI, DC, ALFF, ReHo, ROI-based FC	Resting-state, pre/post-dapoxetine	Altered DC, ALFF, ReHo in bilateral insula; FC altered with precentral, IFG, temporal gyrus, caudate; normalized after dapoxetine	Bilateral insula, precentral gyrus, IFG, middle/inferior temporal gyrus, caudate, ACC; DC, ALFF, ReHo, FC
Yubo M, 2021[18]	17 LPE, 11 HCs	Resting-state fMRI, ALFF	Resting-state, pre/post-dapoxetine	PE: lower ALFF in hippocampus and thalamus, higher in fusiform and lingual gyrus; normalized after dapoxetine	Bilateral hippocampus, thalamus, left fusiform, lingual gyrus; ALFF
Gao S, 2025[19]	90 LPE, 45 HCs	Resting-state fMRI, VMHC	Resting-state	Trait/state anxiety PE: altered VMHC in DMN, AN, SCN; correlations with PEDT/STAI	DMN, AN, SCN; VMHC
Yuan J, 2025[20]	46 LPE, 35 HCs	Resting-state fMRI, PerAF	Resting-state	Increased/decreased PerAF in several regions; correlated with neurotransmitter systems	MCC, supramarginal gyrus, Rolandic operculum, ParaHIPP/HIPP, insula, precuneus, inferior temporal + occipital cortex
Zhou F, 2024[21]	36 LPE, 22 HCs	Resting-state fMRI, surface-based DC	Resting-state	Decreased DC in left precuneus, increased DC in right SMA; DC correlated with IELT/CIPE	Left precuneus, right SMA; surface-based DC
Zhang X, 2024[22]	30 LPE (with depression), 30 PE (without depression), 29 HCs	Resting-state fMRI, graph theory	Resting-state	Altered degree centrality and global efficiency depending on depression status	Right pallidum, right thalamus, right precuneus
Xing S Y, 2023[23]	36 LPE, 22 HCs	Resting-state fMRI, surface-based ReHo and FC	Resting-state	Decreased ReHo in left triangular IFG, increased ReHo in right middle frontal gyrus; FC correlated with PEDT/IELT	Left triangular IFG, right middle frontal gyrus, left lingual gyrus, right orbital superior frontal gyrus; ReHo and FC
Geng B, 2022[24]	42 LPE, 30 HCs	Resting-state fMRI, NAcc-seed FC	Resting-state	Decreased FC between NAcc and thalamus, STC, IFG, OFC, caudate, putamen; FC correlated with PEDT/IELT	NAcc, thalamus, STC, IFG, OFC, caudate, putamen; FC
Gao M, 2022[25]	50 LPE, 40 HCs	Resting-state fMRI, seed-based FC	Resting-state	Decreased thalamocortical FC between motor, prefrontal, temporal cortex, and thalamus; correlations with PEDT/IELT	Thalamus, motor cortex, prefrontal cortex, temporal cortex, posterior parietal cortex, somatosensory cortex, occipital lobe; FC
Chen J, 2022[26]	24 LPE, 23 APE, 44 HCs	DTI, graph theory	Resting-state	Altered clustering coefficient and local efficiency in PE; AMYG.L differentiates primary vs acquired PE	Left IFG, left precentral gyrus, left amygdala

(Continued)

Table 1. Continued.

Authors	Sample	Method	Task/condition	Key findings	Brain regions/metrics
Zhang T, 2022[27]	28 LPE, 28 ED, 28 HCs	Structural MRI, DTI, graph theory	Resting-state	Decreased integration in right middle frontal gyrus (orbital) common to ED and LPE	Right middle frontal gyrus (orbital)
Xu Y, 2021[28]	27 LPE patients with stable emotion (SPE), 27 LPE patients with abnormal emotion (NPE), 30 HCs	Resting-state fMRI, FC analysis	Resting-state	Increased FC between left medial superior frontal gyrus (SFGmed) and amygdala in SPE; FC values correlated with PEDT and EPQ-N	Left SFGmed, amygdala, superior temporal gyrus; FC
Chen J, 2021[29]	18 sPE, 17 nsPE, 24 HCs	Resting-state fMRI, ReHo	Resting-state	Abnormal ReHo in DMN, AUD, AN; sPE: increased AUD, decreased DMN	Temporal, cingulate, parietal cortex; DMN, AUD, AN; ReHo
Gao M, 2021[30]	45 LPE, 37 HCs	Resting-state fMRI, degree centrality (DC)	Resting-state	Increased DC in mPFC, precuneus, SI; decreased in insula, OFC; SI DC correlated with PEDT	mPFC, precuneus, primary somatosensory cortex, insula, OFC; DC
Liu S, 2021[31]	20 LPE with anxiety, 25 HCs	Resting-state fMRI, fALFF	Resting-state	Increased fALFF in right IFG (opercular) and middle frontal gyrus; correlated with PEDT and SAS	Right IFG (opercular), middle frontal gyrus; fALFF
Geng B, 2021[32]	44 LPE, 31 HCs	Resting-state fMRI, VBM and FC	Resting-state	Decreased amygdala volume; altered FC with precuneus, PCC, MTC; correlations with IELT	Bilateral amygdala, precuneus, PCC, MTC; gray matter volume and FC
Gao S, 2021[33]	32 LPE, 38 HCs	DTI and resting-state fMRI, graph theory, and FC	Resting-state	Increased nodal strength in frontal regions, decreased in left amygdala; abnormal FC in DMN and attention network; correlations with PEDT/IELT	Prefrontal cortex, amygdala, DMN, visual recognition network, subcortical network, attention network; SC and FC
Feng N, 2021[34]	34 LPE, 30 HCs	Resting-state fMRI, VMHC	Resting-state	Increased interhemispheric VMHC in multiple regions; correlations with IELT; caudate key node	Precentral gyrus, SI, SMA, precuneus, MTC, STP, thalamus, caudate, MCC; VMHC
Lu J, 2021[35]	36 LPE, 23 HCs	Resting-state fMRI, DFC analysis	Resting-state	Altered reoccurrence times and transition frequencies of DFC states; machine learning classifier distinguished LPE from controls	Functional connectivity metrics (DFC states, reoccurrence times, transitions)
Chen J, 2020[36]	17 LPE, 20 AJ, 23 HCs	Resting-state fMRI, ALFF	Resting-state	PE: increased ALFF in frontal and putamen regions; distinct ALFF patterns from AJ; ALFF correlated with PEDT	Left anterior cingulate, pre/postcentral gyrus, paracentral lobule, superior temporal gyrus, calcarine fissure, putamen, right inferior frontal gyrus; ALFF
Zhang T, 2020[37]	25 LPE, 21 HCs	Resting-state fMRI, structural MRI	Resting-state	Functional hyperconnectivity in MTG subregions; no GMV differences	MTG subregions (anterior, middle, posterior, sulcus), right cuneus, right parahippocampal gyrus, left MTG
Gao M, 2020[38]	47 LPE, 30 HCs	Resting-state fMRI	Resting-state	Altered striatum-related FC; correlations with PEDT	Right caudate, insula, STP, OFC, bilateral putamen, MCC, fusiform
Gao M, 2020[39]	47 LPE, 30 HCs	Resting-state fMRI	Resting-state	Decreased hypothalamus-seeded FC in multiple regions; correlations with IELT	Hypothalamus, OFC, insula, STC, STP, MTC, fusiform, parahippocampal gyrus, cerebellum
Xu Z, 2019[40]	60 non-medicated LPE, 60 HCs	Resting-state fMRI, machine learning	Resting-state	Four key FCs distinguish LPE from HCs, including mOFC-mOFC, rectus-postcentral, insula-pallidum, temporal pole-temporal gyrus	mOFC, rectus, postcentral gyrus, insula, pallidum, temporal pole, temporal gyrus; FC
Lu J, 2018[41]	20 LPE, 15 HCs	Resting-state fMRI, FCD, network topology	Resting-state	Decreased SFCD, increased LFCD; network hubs altered	Middle temporal gyrus, orbitofrontal cortex, nucleus accumbens, fusiform, caudate, thalamus, insula, SMA, cingulate cortex

(Continued)

Table 1. Continued.

Authors	Sample	Method	Task/condition	Key findings	Brain regions/metrics
Guo F, 2018[42]	32 LPE, 31 HCs	Structural MRI, cortical thickness	Resting-state	Thicker cortex in PE patients; correlations with PEDT and disease duration	Frontal, parietal, occipital lobes, limbic system, right medial OFC, right precentral gyrus, left superior frontal cortex, left caudal middle frontal cortex
Yuan J, 2025[43]	47 LPE, 34 HCs	T1-weighted MRI, source-based morphometry	Structural MRI	GMV abnormalities in DMN, PFC, temporal lobe; correlated with neurotransmitters	Default mode network, PFC, temporal lobe
Gao S, 2024[44]	50 LPE, 50 HCs	VBM	Structural MRI	Decreased GMV in DLPFC and thalamus; increased GMV in middle cingulate gyrus	Right dorsolateral superior frontal gyrus, left thalamus, left middle cingulate gyrus
Wu J, 2022[45]	43 LPE, 31 HCs	T1-weighted MRI, structural covariance	Structural MRI	Decreased GMV in caudate and putamen; altered striatum covariance patterns	Bilateral caudate, bilateral putamen, thalamus, amygdala, insula, ACC, MCC, mPFC, primary motor cortex, precuneus/cuneus
Geng B, 2022[46]	52 LPE, 36 HCs	Multimodal MRI, SVM	Structural and functional MRI, DTI	SVM classifier identified key brain abnormalities; high accuracy	Multiple structural, functional, DTI networks
Chen J, 2021[47]	16 LPE with depression, 16 LPE without depression, 32 HCs	DTI, graph theory, structural connectivity	Structural connectivity	PE with depression: altered nodal degree, betweenness, participation in ORBmid.R, PCG, ROL, PoCG, SMG, IPL	Fronto-cingulate-parietal control network; DTI nodal metrics
Xia J D, 2021[48]	20 LPE, 15 HCs	^{1}H-MRS, DTI, volumetric	Structural MRI	Increased Glu and Glu/Cr in thalamus; correlated with clinical scores	Thalamus
Lu J, 2020[49]	23 LPE, 16 HCs	Structural MRI, gyrification index	Structural MRI	Outward deformations in subcortical surfaces; cortical complexity increased	Left hippocampus, bilateral thalamus, right OFC, right nucleus accumbens
Chen J, 2020[50]	32 LPE, 35 HCs	DTI, graph theory	Structural MRI	Altered nodal measures and hub regions in cortico-subcortical network	Right superior frontal gyrus, right inferior frontal gyrus, right rolandic operculum, left insula, right caudate, 7 cortical +2 subcortical hub regions
Chen J, 2020[51]	21 LPE patients with high sympathetic activity, 27 HCs	DTI, graph theory	Structural MRI	Decreased local efficiency in subcortical regions; correlation with PEDT and anxiety	Left amygdala, right pallidum, right thalamus, rolandic operculum, supramarginal gyrus, Heschl gyrus, inferior temporal gyrus
Atalay HA, 2019[52]	54 LPE, 42 HCs	VBM	Structural MRI	Increased caudate nucleus volume in LPE; correlated with PEDT and IELT	Caudate nucleus
Gao M, 2018[53]	32 LPE, 32 HCs	DTI, TBSS	Structural MRI	Widespread FA and axial diffusivity increases; correlated with PEDT	Posterior thalamic radiation, posterior corona radiata, posterior limb of internal capsule, superior corona radiata, external capsule

ACC, anterior cingulate cortex; AJ, anejaculation; ALFF, amplitude of low-frequency fluctuations; AMYG.L, left amygdala; AN, attention network; AN, attention network; APE, acquired premature ejaculation; AUD, auditory network; CIPE, Chinese Index of Premature Ejaculation; CSD, current source density; DC, degree centrality; DFC, dynamic functional connectivity; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; DTI, diffusion tensor imaging; EPQ-N, Eysenck Personality Inventory about neuroticism; FA, fractional anisotropy; fALFF, fractional amplitude of low-frequency fluctuation; FC, functional connectivity; FCD, functional connectivity density; fMRI, Functional Magnetic Resonance Imaging; GMV, gray matter volume; HCs, healthy controls; HIPP, hippocampus; H-MRS, proton magnetic resonance spectroscopy; IELT, intravaginal ejaculatory latency time; IFG, inferior frontal gyrus; IPL, inferior parietal gyrus; LFCD, long-range FCD; LORETA, low-resolution brain electromagnetic tomography; LPE, lifelong premature ejaculation; MCC, middle cingulate cortex; mOFC, medial part of orbital frontal cortex; mPFC, medial prefrontal cortex; MTC, middle temporal cortex; MTG, middle temporal gyrus; NAcc, nucleus accumbens; nsPE, PE patients with normal sympathetic activity; OFC, orbitofrontal cortex; ORBmid.R, right middle frontal gyrus (orbital part); PCC, posterior cingulate cortex; PCG, posterior cingulate gyrus; PEDT, premature ejaculation diagnostic tool; PerAF, Percent Amplitude of Fluctuation; PFC, prefrontal cortex; PoCG, postcentral gyrus; ReHo, regional homogeneity; ROL, rolandic operculum; SAS, self-rating anxiety scale; SC, structural connectivity; SCN, subcortical network; SFCD, short-range FCD; SFGmed, medial superior frontal gyrus; SI, somatosensory cortex; SMA, supplementary motor area; SMG, supramarginal gyrus; sPE PE, patients with high sympathetic activity; SSRT, stop signal reaction time; STAI, state and trait anxiety inventory; STC, superior temporal cortex; STP, superior temporal pole; SVM, support vector machine; TBSS, tract-based spatial statistical analysis; VBM, voxel-based morphometry; VMHC, voxel-mirrored homotopic connectivity.

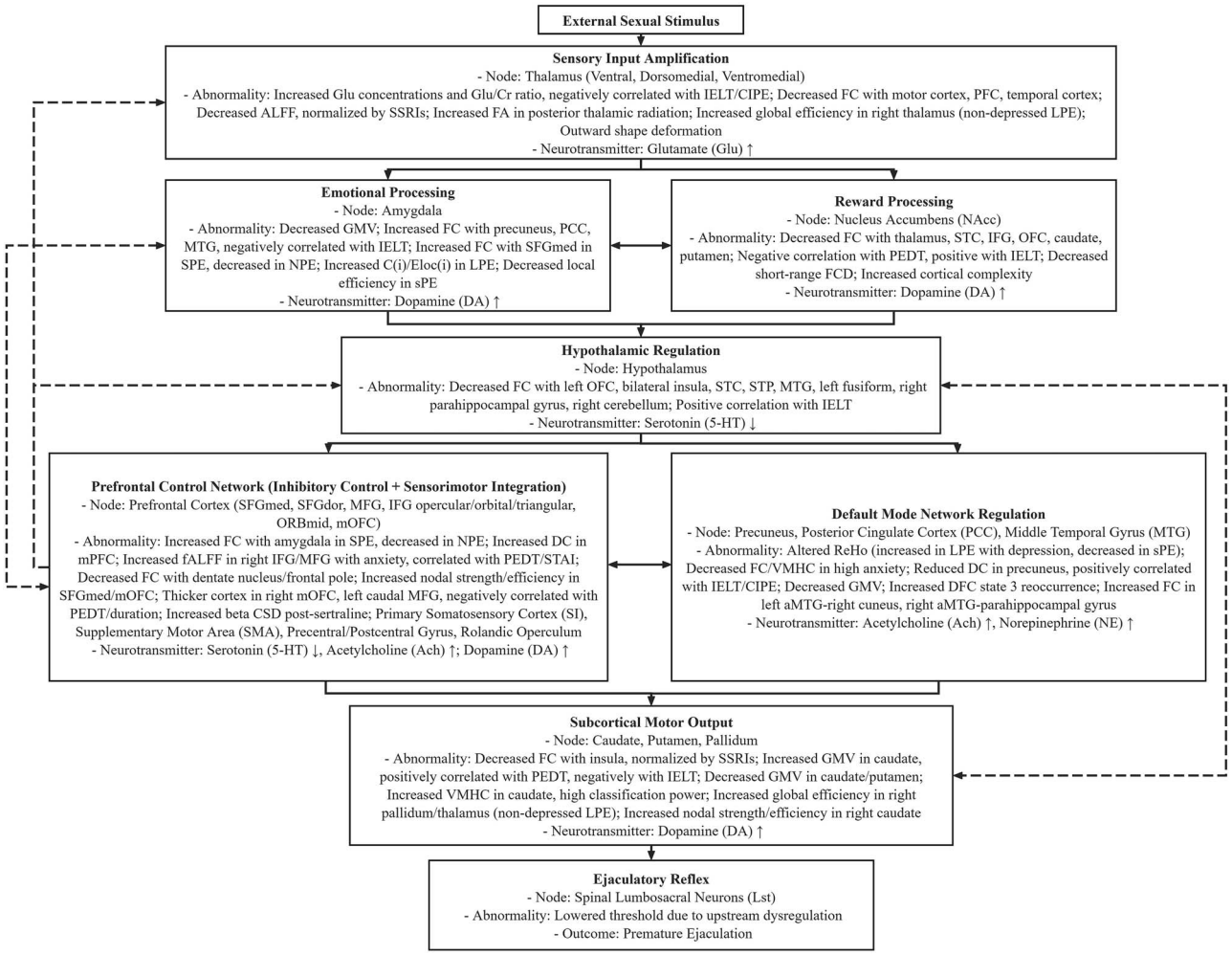

Figure 1. Integrative neural model of lifelong premature ejaculation based on 43 neuroimaging and electrophysiological studies. Solid black arrows indicate the primary bottom-up processing flow from sensory input to ejaculatory reflex. Dashed black arrows represent feedback loops reflecting top-down or modulatory control between cortical, limbic, and subcortical regions. Note: Full forms of the acronyms appearing in this figure are provided in the acronym list.

characterized by abnormal degree centrality and global efficiency,[22] implying that affective modulation further perturbs ejaculatory control networks.

Neurochemical and multimodal insights

Recent multimodal studies have begun to integrate neurotransmitter mapping with neuroimaging metrics. Altered percent amplitude of fluctuation (PerAF) was observed in the insula, middle cingulate cortex, supramarginal gyrus, and parahippocampal regions, and these functional abnormalities correlated spatially with dopaminergic, cholinergic, and adrenergic systems.[20] Collectively, these findings indicate that serotonergic and dopaminergic dysregulation may jointly modulate the neural excitability of regions critical for sensory, emotional, and inhibitory control of ejaculation.

In summary, neuroimaging studies demonstrate that LPE involves decreased prefrontal and parietal inhibitory control, hyper-responsivity within limbic and temporal emotional circuits, disrupted integration across hypothalamic–striatal–cortical pathways, and neurochemical imbalances in serotonergic and dopaminergic systems. Collectively, these findings provide a multilevel neural framework for understanding the central mechanisms underlying ejaculatory dysregulation.

Electrophysiological evidence

Electrophysiological investigations using EEG have provided complementary evidence for abnormal cortical excitability and information processing in PE, capturing the temporal dynamics of neural dysfunction not accessible by fMRI.

Altered cortical activation and inhibitory control

Early EEG studies demonstrated reduced alpha-band power and altered cortical source activity in the right precentral gyrus, insula, and superior parietal lobules during erotic stimulation in PE patients compared with controls.[11] These changes suggest decreased cortical inhibition and disrupted sensory integration during sexual arousal.

Subsequent work by Kwon et al.[16] further showed that administration of sertraline, a SSRI, increased high–beta–band current source density in the superior and medial frontal gyri—regions implicated in executive control and inhibitory regulation—while decreasing activation in occipitotemporal visual areas. This pattern indicates that serotonergic modulation may enhance prefrontal inhibitory activity and normalize cortical processing during erotic stimulation in men with PE, providing electrophysiological evidence for the central inhibitory mechanism of SSRI treatment.

Synthesis of evidence

Across modalities, the collective evidence supports a dual-pathway model of the neurobiology of LPE. This model encompasses deficient prefrontal–striatal inhibitory control, which correlates with the suppression of ejaculatory reflexes, and hyperresponsive limbic–temporal sensory circuits, which mirrors the increase in the arousal and acceleration of the reflex activation. These central abnormalities likely interact with serotonergic and dopaminergic dysregulation, exacerbating the rapid ejaculation and reducing volitional control, the two major characteristic of LPE. Taken together, findings from neuroimaging and electrophysiological studies converge to conceptualize LPE as a disorder correlated with impaired top-down regulation and coupled with excessive bottom-up arousal (Figure 1).

Discussion

Summary of key findings

This narrative review synthesizes evidence from 43 original neuroimaging and electrophysiological studies, highlighting that LPE is associated with widespread alterations across prefrontal, striatal, limbic, thalamic, and temporal regions, encompassing both structural and functional abnormalities. Neuroimaging studies demonstrate decreased gray matter volume[32,43,52] and altered cortical thickness in prefrontal and orbitofrontal regions,[42] reflecting impaired top-down inhibitory control; microstructural white matter changes in tracts connecting prefrontal, striatal, and limbic regions,[53] indicating disrupted information integration; altered connectivity within cortico-striatal–limbic circuits, characterized by reduced prefrontal and insular regulation and abnormal engagement of limbic and temporal regions[17]; and neurochemical abnormalities, particularly in serotonergic and dopaminergic pathways,[20,43] which correlate with clinical severity as measured by premature ejaculation diagnostic tool (PEDT) scores. Complementing these findings, electrophysiological studies indicate altered cortical activity in frontal, temporal, and parietal regions during sexual arousal, reflecting disrupted inhibitory processing.[11,16] Collectively, these results suggest that LPE is not merely a peripheral or psychological disorder, but may involve a complex neurobehavioral condition produced by a dysregulated top-down control and exaggerated bottom-up arousal.

Theoretical interpretation

The convergent evidence supports a dual-pathway model of ejaculatory control, incorporating both top-down inhibitory deficits and bottom-up hyperexcitability. Dysfunction in the prefrontal cortex—especially the dorsolateral, medial, and orbital regions—reduces the ability to suppress spinal ejaculatory reflexes, while altered connectivity between prefrontal, striatal (caudate and putamen), and thalamic regions underpins impaired inhibitory control.[27,41,43] Subcortical structures including the amygdala, hippocampus, and hypothalamus also show structural and functional abnormalities, contributing to dysregulated ejaculatory timing and heightened sympathetic activity.[26,39,52]

Concurrently, enhanced sensory processing in temporal, parietal, and insular cortices, as well as hyperconnectivity in the middle cingulate and MTG subregions, accelerates sexual arousal and ejaculatory response, consistent with reduced cortical gating observed in EEG, fMRI, and PerAF studies.[16,20,37] White matter microstructural changes, including altered fractional anisotropy in thalamocortical and striatocortical pathways, further indicate impaired signal conduction efficiency.[50,53]

These neural dynamics are modulated by neurochemical imbalances, including serotonergic hypofunction, dopaminergic hyperactivity, and alterations in acetylcholine and epinephrine pathways, providing a mechanistic basis for the efficacy of SSRIs in increasing the ejaculatory control[54-56] and in prolonging IELT.[20,41] Importantly, multimodal imaging studies, combining structural MRI, DTI, fMRI, and machine learning analyses, reveal that PE reflects distributed network dysfunction spanning cortical and subcortical systems, emphasizing the need for integrative, network-based models rather than simplistic lesion-based explanations.[35,46]

Clinical implications

The neuroimaging findings summarized in this review provide valuable insights into the central mechanisms that may underlie LPE. However, their current clinical applicability remains limited, and diagnosis should continue to rely primarily on clinical history, patient-reported symptoms, and standardized questionnaires, rather than neuroimaging or electrophysiological tools. Although structural and functional alterations in prefrontal–striatal–limbic circuits correlate with PEDT scores and IELT in several studies,[27,35,38,43] these associations should be interpreted as research-level observations, not as objective biomarkers suitable for routine clinical assessment. At present, neuroimaging cannot reliably determine the presence or severity of LPE at an individual level.

Despite these limitations, several potential translational implications can be cautiously considered. Interventions targeting these circuits—such as cognitive-behavioral therapy, emotion regulation training, or neuromodulation aimed at enhancing prefrontal inhibitory control and modulating limbic hyperactivity[13,37,39]—may complement pharmacotherapy.[57] Similarly, neuromodulation techniques designed to change prefrontal regulatory function remain conceptually promising,[58] but empirical validation in LPE is still lacking. Pharmacologically, SSRIs are thought to exert therapeutic effects by restoring serotonergic tone within prefrontal–limbic networks, consistent with observed prefrontal hypoactivity and striatal–limbic hyperresponsiveness,[16,20,59] as early pointed out[60]; future strategies may also consider dopaminergic modulation or targeting GABAergic/glutamatergic balance based on individualized neural profiles.[41,53] Multimodal neuroimaging studies employing machine learning and support vector machines have demonstrated high accuracy in distinguishing LPE patients from controls,[35,46] but findings remain preliminary due to relatively small sample sizes. Their relevance to individualized clinical decision-making is therefore limited and premature. At this stage, such approaches should be viewed as exploratory tools for understanding pathophysiology, not as precursors to clinically actionable diagnostic systems. Overall, while neuroimaging research enriches our understanding of the central mechanisms implicated in LPE, its clinical impact is currently modest, and future longitudinal, adequately powered studies are essential before any translational applications can be responsibly considered.

Critical approach to the neurobiological evidence on LPE

Marcel Waldinger's early work helped bring biological mechanisms of PE into scientific focus.[61] Waldinger believed that PE is the result of a congenital alteration of the serotonin pathway, with a genetic basis that has been long sought, without ever yielding definitive results in humans.[62] The intent was certainly virtuous, even if it resulted in an oversimplification of a complex and multifaceted symptom like PE and ultimately led research down a blind alley. The unconvincing data may have arisen from the apodictic certainty that the simplistic temporal characterization of PE can identify two homogeneous groups of patients: LPE versus APE. Phenotypic heterogeneity poses a methodological challenge for neuroimaging research on LPE. Individuals may present with persistent, lifelong-onset ejaculatory symptoms driven primarily by psychosocial or contextual factors, yet meet diagnostic criteria for LPE.[63] Without rigorous phenotyping, such cases may introduce noise into neurobiological analyses and confound mechanistic interpretations. While almost all PE studies have been claimed to be performed on heterosexual populations, a psychometric tool, such as XYGO, to stratify patients according to sexual orientation and gender identity has never been used yet.[64] Strangely, the issue of homogeneity in the experimental sample has received little attention in studies on PE. For example, it has been only very recently demonstrated that severity LPE could be classified on the different outcomes of the PEDT.[65]

Despite these biases, the merit of the neurobiological approach has been enormous. This line of inquiry—the search for the biological basis of sexual behavior and, in particular, ejaculatory disorders—has since been continued and expanded by numerous independent research groups.[66]

The problem of sampling homogeneity could be in the future overcome by comparing two populations: for example, those with LPE versus those with APE, or those with clinical PE versus those with subclinical PE (a condition easily recognizable using major and minor criteria), or those with "pure" PE versus those with loss of erectile and ejaculatory control, a condition occurring in up to 50% of patients with PE.[67] This strategy could also be useful for better understanding another issue raised by the studies reviewed here: that of cause–effect relationships.

In fact, a second major point should be considered when evaluating the important studies here summarized. Brain is likely the most plastic human tissue and its morphology is largely dependent on the experience and on behaviors. Hence, while the central alterations here described could potentially cause LPE, they could be consequences of the chronic inability to control ejaculation generated by several known and yet unknown causes. The impossibility of establishing a causative relationship is not rare in neurobiological studies.

The third limit is also methodological. Most studies feature relatively small sample sizes, limiting the generalizability of findings. Cross-sectional designs predominate, making it difficult to establish causality or to disentangle predisposing traits from compensatory adaptations, as pointed out above. Multimodal integration remains sparse, with few studies combining structural, functional, and neurochemical measures. Moreover, sexual and psychological context is often insufficiently controlled, and comorbidities such as anxiety and depression may confound neural findings. It is noteworthy that most neuroimaging studies on LPE have been conducted in China, while evidence from other regions remains limited. This geographical concentration may affect the generalizability and external validity of current findings. Future research should involve multicenter and cross-cultural collaborations.

However, all those limits, frequently experienced in the young field of sexual medicine when "boldly go(ing) where no man has gone before,"[68] should not decrease the interest in the neurobiology of PE. The central morphological and functional alterations here described, even in the case we assume that are not the (unique) etiology of LPE, should be regarded as a major contributing factor, amplifying, exacerbating, and making chronic the inability to control ejaculation in some patients affect by PE. In fact, it is evident that the consistent demonstration of central alterations in LPE, thanks to large production of original and new data, is the most hectic, active, and promising subfield in contemporary PE research.

Future directions

Future research should prioritize longitudinal, multimodal imaging studies to track neural changes before and after treatment and comparison of the findings obtained in different homogeneous subsets of patients. Network-based and computational modeling approaches are needed to quantify the interactions between top-down inhibitory and bottom-up excitatory processes underlying ejaculatory control. Integrating neurochemical imaging techniques, such as PET and proton magnetic resonance spectroscopy, with structural and functional MRI could elucidate how neurotransmitter dynamics relate to network dysfunction. Additionally, developing personalized neuromodulatory or pharmacological interventions guided by neural biomarkers may enhance treatment efficacy. Finally, employing sexually relevant ecological paradigms in fMRI and EEG studies could provide more accurate insights into real-world sexual behavior and associated neural responses.

Conclusions

Collectively, neuroimaging and electrophysiological studies support a central neural involvement in LPE, characterized by impaired prefrontal inhibitory control, and dysregulation of serotonergic, dopaminergic, and other neuromodulatory pathways. These neural alterations, that characterize LPE as a cause, a con-cause or an exacerbating consequence, may underlie accelerated sexual arousal and deficient top-down control over spinal ejaculatory reflexes. Importantly, multimodal imaging and machine learning studies suggest that LPE reflects distributed network dysfunction rather than isolated regional lesions, extending classical psychosexual and peripheral hypotheses. This mechanistic framework reflects research-level neural correlates identified in LPE—rather than acquired or secondary forms of PE—and may inform future hypothesis-driven work. Nevertheless, large-scale and longitudinal studies are needed before any diagnostic or therapeutic translation can be considered.

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Author contributions

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Conflicts of interest

E.A.J. is or has been a consultant and/or paid speaker for Bayer, FQM, Ibsa, Kanna, Lundbeck, Menarini, Merck, Mia, Otsuka, Pfizer, Recordati, Shionogi, and Viatris. The other authors declare no competing interests.

References

1. Gao J, Zhang X, Su P, et al. Prevalence and factors associated with the complaint of premature ejaculation and the four premature ejaculation syndromes: a large observational study in China. *J Sex Med*. 2013;**10**(7):1874–1881. https://doi.org/10.1111/jsm.12180
2. Serefoglu EC, Yaman O, Cayan S, et al. The comparison of premature ejaculation assessment questionnaires and their sensitivity for the four premature ejaculation syndromes: results from the Turkish society of andrology sexual health survey. *J Sex Med*. 2011;**8**(4):1177–1185. https://doi.org/10.1111/j.1743-6109.2010.02183.x
3. Colonnello E, Sansone A, Zhang H, Zhang Y, Jannini EA. Towards a universal definition of premature ejaculation. *J Sex Med*. 2022;**19**(12):1717–1720. https://doi.org/10.1016/j.jsxm.2022.05.003
4. Serefoglu EC, McMahon CG, Waldinger MD, et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second international society for sexual medicine ad hoc committee for the definition of premature ejaculation. *Sex Med*. 2014;**2**(2):41–59. https://doi.org/10.1002/sm2.27
5. Waldinger, M.D., *Pathophysiology of Lifelong Premature Ejaculation*. Milano: Springer Milan, 2012: p. 71-80, https://doi.org/10.1007/978-88-470-2646-9_6.
6. Castiglione F, Albersen M, Hedlund P, Gratzke C, Salonia A, Giuliano F. Current pharmacological management of premature ejaculation: a systematic review and meta-analysis. *Eur Urol*. 2016;**69**(5):904–916. https://doi.org/10.1016/j.eururo.2015.12.028
7. Waldinger MD. The neurobiological approach to premature ejaculation. *J Urol*. 2002;**168**(6):2359–2367. https://doi.org/10.1016/S0022-5347(05)64146-8
8. Sansone A, Aversa A, Corona G, et al. Management of premature ejaculation: a clinical guideline from the Italian Society of Andrology and Sexual Medicine (SIAMS). *J Endocrinol Investig*. 2021;**44**(5):1103–1118. https://doi.org/10.1007/s40618-020-01458-4
9. Raisi F, Soleimani R, Ahmadzadeh A, Sadati SN, Fakhrian A, Jalali MM. Efficacy and safety of pharmacological treatments in patients with premature ejaculation: an umbrella review of meta-analyses of randomized controlled trials. *J Sex Med*. 2025;**22**(6):1014–1023. https://doi.org/10.1093/jsxmed/qdaf094
10. Baethge C, Goldbeck-Wood S, Mertens S. SANRA—a scale for the quality assessment of narrative review articles. *Res Integrity Peer Rev*. 2019;**4**(1):5. https://doi.org/10.1186/s41073-019-0064-8
11. Hyun J-S, Kam S-C, Kwon O-Y. Changes of cerebral current source by audiovisual erotic stimuli in premature ejaculation patients. *J Sex Med*. 2008;**5**(6):1474–1481. https://doi.org/10.1111/j.1743-6109.2007.00734.x
12. Lu J, Hu Q, Lei Y, et al. Task modulation of resting-state functional gradient stability in lifelong premature ejaculation: an FMRI study. *eneuro*. 2025;**12**(6):ENEURO.0066–ENEU25.2025. https://doi.org/10.1523/ENEURO.0066-25.2025
13. Yang X, Gao M, Zhang L, et al. Central neural correlates during inhibitory control in lifelong premature ejaculation patients. *Front Hum Neurosci*. 2018;**12**:206. https://doi.org/10.3389/fnhum.2018.00206
14. Bai Y, Chen F, Long C, et al. Glans penis electric stimulation modulates cerebral activity and functional connectivity in lifelong premature ejaculation revealed by functional MRI. *Sci Rep*. 2025;**15**(1):23328. https://doi.org/10.1038/s41598-025-03994-6
15. Zhang B, Lu J, Xia J, et al. Functional insights into aberrant brain responses and integration in patients with lifelong premature ejaculation. *Sci Rep*. 2017;**7**(1):460. https://doi.org/10.1038/s41598-017-00421-3
16. Kwon O, Kam SC, Choi JH, do JM, Hyun JS. Effects of sertraline on brain current source of the high beta frequency band: analysis of electroencephalography during audiovisual erotic stimulation in males with premature ejaculation. *Int J Impot Res*. 2011;**23**(5):213–219. https://doi.org/10.1038/ijir.2011.30
17. Gao M, Geng B, Zhang S, et al. Changes of insular function in lifelong premature ejaculation patients before and after SSRI administration. *Psychopharmacology*. 2022;**239**(12):3953–3962. https://doi.org/10.1007/s00213-022-06268-5
18. Yubo M, Lianjia H, Cuiping M, et al. Changes in the amplitude of low-frequency fluctuation in patients with lifelong premature ejaculation by resting-state functional MRI. *Sex Med*. 2021;**9**(1):100287–100287. https://doi.org/10.1016/j.esxm.2020.100287
19. Gao S, Liu R, Niu P, et al. Neural basis underlying the effects of trait and state anxiety on premature ejaculation revealed by resting-state interhemispheric functional connectivity. *J Affect Disord*. 2025;**389**:119666. https://doi.org/10.1016/j.jad.2025.119666
20. Yuan J, Wang P, Nie D, et al. Abnormal percent amplitude of fluctuation in patients with lifelong premature ejaculation is associated with neurotransmitter profiles. *Brain Imaging Behav*. 2025;**19**(1):41–49. https://doi.org/10.1007/s11682-024-00920-8
21. Zhou F, Wu W, He X, Cao L, Ni L, Lu J. The surface-based degree centrality of patients with lifelong premature ejaculation: a resting-state fMRI study. *Neuroscience*. 2024;**561**:87–91. https://doi.org/10.1016/j.neuroscience.2024.10.026
22. Zhang X, Niu P, Su M, et al. Topological differences of striato-thalamo-cortical circuit in functional brain network between premature ejaculation patients with and without depression. *Brain Behav*. 2024;**14**(6):e3585. https://doi.org/10.1002/brb3.3585
23. Xing S-Y, Lu JM, Jiang YH, et al. Abnormal cortical surface-based spontaneous and functional connectivity in the whole brain in lifelong premature ejaculation patients. *Asian J Androl*. 2023;**25**(6):699–703. https://doi.org/10.4103/aja202349
24. Geng B, Gao M, Wu J, et al. Functional connectivity of nucleus accumbens is associated with lifelong premature ejaculation in male adults: a resting-state fMRI study. *Clin Neuroradiol*. 2022;**32**(3):655–663. https://doi.org/10.1007/s00062-021-01105-2
25. Gao M, Geng B, Jannini TB, et al. Thalamocortical dysconnectivity in lifelong premature ejaculation: a functional MRI

study. *Urology*. 2022;**159**:133–138. https://doi.org/10.1016/j.urology.2021.10.010
26. Chen J, Wang Q, Huang X, et al. Potential biomarkers for distinguishing primary from acquired premature ejaculation: a diffusion tensor imaging based network study. *Front Neurosci*. 2022;**16**:929567. https://doi.org/10.3389/fnins.2022.929567
27. Zhang T, Yuan P, Cui Y, Yuan W, Jiang D. Convergent and divergent structural connectivity of brain white matter network between patients with erectile dysfunction and premature ejaculation: a graph theory analysis study. *Front Neurol*. 2022;**13**:804207. https://doi.org/10.3389/fneur.2022.804207
28. Xu Y, Zhang X, Xiang Z, et al. Abnormal functional connectivity between the left medial superior frontal gyrus and amygdala underlying abnormal emotion and premature ejaculation: a resting state fMRI study. *Front Neurosci*. 2021;**15**:704920. https://doi.org/10.3389/fnins.2021.704920
29. Chen J, Wu W, Xiang Z, et al. Aberrant default mode network and auditory network underlying the sympathetic skin response of the penis (PSSR) of patients with premature ejaculation: a resting-state fMRI study. *Andrology*. 2021;**9**(1):277–287. https://doi.org/10.1111/andr.12914
30. Gao M, Feng N, Liu X, et al. Abnormal degree centrality in lifelong premature ejaculation patients: an fMRI study. *Brain Imaging Behav*. 2021;**15**(3):1412–1419. https://doi.org/10.1007/s11682-020-00340-4
31. Liu S, Zhang X, Wang Q, et al. Increased attentional network activity in premature ejaculation patients with anxiety revealed by resting-state functional magnetic resonance imaging. *Eur J Neurosci*. 2021;**54**(4):5417–5426. https://doi.org/10.1111/ejn.15402
32. Geng B, Gao M, Wu J, et al. Smaller volume and altered functional connectivity of the amygdala in patients with lifelong premature ejaculation. *Eur Radiol*. 2021;**31**(11):8429–8437. https://doi.org/10.1007/s00330-021-08002-9
33. Gao S, Chen J, Xu Y, et al. Altered structural and functional connectivity contribute to rapid ejaculation: insights from a multimodal neuroimaging study. *Neuroscience*. 2021;**471**:93–101. https://doi.org/10.1016/j.neuroscience.2021.06.034
34. Feng N, Gao M, Wu J, Yang G, Piao R, Liu P. Higher interhemispheric homotopic connectivity in lifelong premature ejaculation patients: a pilot resting-state fMRI study. *Quant Imaging Med Surg*. 2021;**11**(7):3234–3243. https://doi.org/10.21037/qims-20-1103
35. Lu J, Chen Q, Li D, et al. Reconfiguration of dynamic functional connectivity states in patients with lifelong premature ejaculation. *Front Neurosci*. 2021;**15**:721236. https://doi.org/10.3389/fnins.2021.721236
36. Chen J, Yang J, Huang X, et al. Brain functional biomarkers distinguishing premature ejaculation from anejaculation by ALFF: a resting-state fMRI study. *J Sex Med*. 2020;**17**(12):2331–2340. https://doi.org/10.1016/j.jsxm.2020.09.002
37. Zhang T, Tang D, Cai H, et al. Selective functional hyperconnectivity in the middle temporal gyrus subregions in lifelong premature ejaculation. *J Sex Med*. 2020;**17**(8):1457–1466. https://doi.org/10.1016/j.jsxm.2020.05.006
38. Gao M, Feng N, Guo B, et al. Striatum-related intrinsic connectivity deficits in lifelong premature ejaculation patients. *Urology*. 2020;**143**:159–164. https://doi.org/10.1016/j.urology.2020.06.001
39. Gao M, Feng N, Wu J, et al. Altered functional connectivity of hypothalamus in lifelong premature ejaculation patients. *J Magn Reson Imaging*. 2020;**52**(3):778–784. https://doi.org/10.1002/jmri.27099
40. Xu Z, Yang X, Gao M, et al. Abnormal resting-state functional connectivity in the whole brain in lifelong premature ejaculation patients based on machine learning approach. *Front Neurosci*. 2019;**13**:448. https://doi.org/10.3389/fnins.2019.00448
41. Lu J, Zhang X, Wang H, et al. Short- and long-range synergism disorders in lifelong premature ejaculation evaluated using the functional connectivity density and network property. *NeuroImage Clin*. 2018;**19**:607–615. https://doi.org/10.1016/j.nicl.2018.05.025
42. Guo F, Xi YB, Gao M, et al. Alterations in cortical thickness in nonmedicated premature ejaculation patients: a morphometric MRI study. *J Magn Reson Imaging*. 2018;**47**(3):656–662. https://doi.org/10.1002/jmri.25808
43. Yuan J, Wang P, Feng J, et al. Brain structural changes in lifelong premature ejaculation patients: insights from multivariate and neurotransmitter analyses. *J Sex Med*. 2025;**22**:1958–1966. https://doi.org/10.1093/jsxmed/qdaf262
44. Gao S, Chen J, Liu J, et al. Decreased grey matter volume in dorsolateral prefrontal cortex and thalamus accompanied by compensatory increases in middle cingulate gyrus of premature ejaculation patients. *Andrology*. 2024;**12**(4):841–849. https://doi.org/10.1111/andr.13547
45. Wu J, Gao M, Piao R, Feng N, Geng B, Liu P. Magnetic resonance imaging-based structural covariance changes of the striatum in lifelong premature ejaculation patients. *J Magn Reson Imaging*. 2022;**55**(2):443–450. https://doi.org/10.1002/jmri.27851
46. Geng B, Gao M, Piao R, et al. Multivariate pattern analysis of lifelong premature ejaculation based on multiple kernel support vector machine. *Front Psych*. 2022;**13**:906404. https://doi.org/10.3389/fpsyt.2022.906404
47. Chen J, Yang J, Xiang Z, et al. Graph theory analysis reveals premature ejaculation is a brain disorder with altered structural connectivity and depressive symptom: a DTI-based connectome study. *Eur J Neurosci*. 2021;**53**(6):1905–1921. https://doi.org/10.1111/ejn.15048
48. Xia J-D, Chen F, Zhang QJ, et al. Abnormal thalamic metabolism in patients with lifelong premature ejaculation. *J Sex Med*. 2021;**18**(2):275–283. https://doi.org/10.1016/j.jsxm.2020.11.014
49. Lu J, Yuan L, Jin J, et al. Brain cortical complexity and subcortical morphometrics in lifelong premature ejaculation. *Front Hum Neurosci*. 2020;**14**:283. https://doi.org/10.3389/fnhum.2020.00283
50. Chen J, Yang J, Huang X, et al. Variation in brain subcortical network topology between men with and without PE: a diffusion tensor imaging study. *J Sex Med*. 2020;**17**(1):48–59. https://doi.org/10.1016/j.jsxm.2019.10.009
51. Chen J, Huang X, Lu C, et al. Graph analysis of DTI-based connectome: decreased local efficiency of subcortical regions in PE patients with high sympathetic activity. *Andrology*. 2020;**8**(2):400–406. https://doi.org/10.1111/andr.12701
52. Atalay HA, Sonkaya AR, Ozbir S, et al. Are there differences in brain morphology in patients with lifelong premature ejaculation? *J Sex Med*. 2019;**16**(7):992–998. https://doi.org/10.1016/j.jsxm.2019.04.008
53. Gao M, Yang X, Liu L, et al. Abnormal white matter microstructure in lifelong premature ejaculation patients identified by tract–based spatial statistical analysis. *J Sex Med*. 2018;**15**(9):1272–1279. https://doi.org/10.1016/j.jsxm.2018.07.012
54. Hou G, Zhang G, Gao M, et al. The inaugural pre-treatment nomogram to assess the eight-week efficacy of dapoxetine: a prospective multi-Center study. *Andrology*. 2025 Oct 9. https://doi.org/10.1111/andr.70128. Epub ahead of print.
55. Peng J, Yang L, Liu L, et al. Safety and effectiveness of dapoxetine on demand in Chinese men with premature ejaculation: results of a multicenter, prospective, open-label phase IV study. *Sex Med*. 2021;**9**(2):100296–100296. https://doi.org/10.1016/j.esxm.2020.100296
56. Sansone A, Yuan J, Hou G, et al. From Waterloo to the Great Wall: a retrospective, multicenter study on the clinical practice and cultural attitudes in the management of premature ejaculation, China. *Andrology*. 2024;**12**(2):247–258. https://doi.org/10.1111/andr.13403
57. Ciocca G, Limoncin E, Mollaioli D, et al. Integrating psychotherapy and pharmacotherapy in the treatment of premature ejaculation. *Arab J Urol*. 2013;**11**(3):305–312. https://doi.org/10.1016/j.aju.2013.04.011

58. Regenold WT, Deng Z-D, Lisanby SH. Noninvasive neuromodulation of the prefrontal cortex in mental health disorders. *Neuropsychopharmacology*. 2022;**47**(1):361–372. https://doi.org/10.1038/s41386-021-01094-3
59. Jannini TB, Lorenzo GD, Bianciardi E, et al. Off-label uses of selective serotonin reuptake inhibitors (SSRIs). *Curr Neuropharmacol*. 2022;**20**(4):693–712. https://doi.org/10.2174/1570159X19666210517150418
60. Jannini EA, Simonelli C, Lenzi A. Disorders of ejaculation. *J Endocrinol Investig*. 2002;**25**(11):1006–1019. https://doi.org/10.1007/BF03344077
61. McMahon CG. Obituary for Marcel Waldinger. *J Sex Med*. 2019;**16**(8):1125–1127. https://doi.org/10.1016/j.jsxm.2019.05.014
62. van Raaij JJ, Serefoglu EC, van Amelsvoort TAMJ, Janssen PKC. Possible pathophysiologic roles of neurotransmitter systems in men with lifelong premature ejaculation: a scoping review. *Sex Med Rev*. 2024;**12**(4):638–651. https://doi.org/10.1093/sxmrev/qeae048
63. Corona G, Cucinotta D, di Lorenzo G, et al. The Italian Society of Andrology and Sexual Medicine (SIAMS), along with ten other Italian Scientific Societies, guidelines on the diagnosis and management of erectile dysfunction. *J Endocrinol Investig*. 2023;**46**(6):1241–1274. https://doi.org/10.1007/s40618-023-02015-5
64. Di Cristofaro A, Jannini TB, Colonnello E, et al. XYGO: proposing a new holistic measure of gender identity and sexual orientation. *Nat Rev Urol*. 2025;**22**:387–405. https://doi.org/10.1038/s41585-025-01041-7
65. Zhong Q, Wang C, Zhu D, et al. The severity classification of lifelong premature ejaculation based on the premature ejaculation diagnostic tool. *Andrology*. 2025 Sept 25. https://doi.org/10.1111/andr.70124. Epub ahead of print.
66. Ma D, Wang H, Colonnello E, et al. Trends in premature ejaculation research from 2004 to 2023: a bibliometric analysis. *Andrologia*. 2025;**2025**(1):9984316. https://doi.org/10.1155/and/9984316
67. Colonnello E, Ciocca G, Limoncin E, Sansone A, Jannini EA. Redefining a sexual medicine paradigm: subclinical premature ejaculation as a new taxonomic entity. *Nat Rev Urol*. 2021;**18**(2):115–127. https://doi.org/10.1038/s41585-020-00417-1
68. Day D. Boldly going: star trek and spaceflight. *Space Rev*. 2005;**28**:1–16.

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https://doi.org/10.1093/sxmrev/qeaf075
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