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RESEARCH

Abnormal percent amplitude of fluctuation in patients with lifelong premature ejaculation is associated with neurotransmitter profiles

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Abstract

Identifying additional imaging biomarkers of lifelong premature ejaculation (LPE) may provide valuable insights into understanding the underlying neural mechanisms of this disorder. Forty-six LPE patients and thirty-five healthy controls (HCs) were enrolled in this study. The Percent Amplitude of Fluctuation (PerAF) method was used to assess differences in brain function in LPE patients compared to HCs during the resting-state. Receiver operating characteristic (ROC) analysis was used to investigate the potential biomarkers based on the imaging findings. Correlation analysis was then applied to examine the relationships between the neuroimaging findings and clinical symptoms. We also investigated whether PerAF alterations in LPE patients were associated with specific neurotransmitter systems. Compared to HCs, LPE patients showed increased PerAF in the middle cingulate cortex (MCC), supramarginal gyrus, Rolandic operculum, parahippocampus/hippocampus (ParaHIPP/HIPP) as well as insula; and decreased PerAF in the precuneus, inferior temporal cortex plus occipital cortex. The MCC and ParaHIPP/HIPP exhibited higher classification performance on ROC analysis. Positive correlations were found between the Premature Ejaculation Diagnostic Tool score and PerAF in the insula, and the International Index of Erectile Function score and PerAF in the precuneus. Additionally, altered PerAF in LPE patients correlated significantly with the spatial distribution of dopamine, acetylcholine and epinephrine pathways. Our findings indicate that LPE patients have PerAF-related changes in certain brain regions associated with visual, sensory and/or emotional processing, and reveal that the abnormal control of ejaculatory function may be related to the combined dysregulation of neurotransmitter systems in LPE patients.

Keywords Lifelong premature ejaculation · Percent amplitude of fluctuation · Magnetic resonance imaging · Neurotransmitter

Introduction

Premature ejaculation (PE) is a prevalent sexual dysfunction in men. Based on epidemiological data, the International Society for Sexual Medicine (ISSM) estimates

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that approximately 5% of men worldwide suffer from PE (Althof et al., 2014), with a prevalence of 7.8% in China (Gao et al., 2013). Within this Chinese population, lifelong premature ejaculation (LPE) accounts for approximately 3%. LPE is defined by the ISSM committee as "always or almost always ejaculation occurring before vaginal penetration or within approximately 1 minute of initial sexual intercourse" (Althof et al., 2014). The prevalence of LPE and the enormous psychological trauma it causes in patients result in a serious medical and economic burden on individuals and society. Currently, the complex pathogenesis and neurophysiological mechanism of LPE remain unclear, with a combination of psychological and biological factors (Atalay et al., 2019). Moreover, the diagnosis of LPE mainly relies on various scales and questionnaires, with a notable lack of objective biomarkers.

Over the past decades, it has been acknowledged that alterations in brain function are associated with LPE (Gao et al., 2022). Resting-state functional magnetic resonance imaging (fMRI) has been increasingly applied to evaluate possible abnormalities of brain functions in LPE patients (Liu et al., 2021). For example, compared to healthy controls (HCs), LPE patients showed altered Amplitude of Low-Frequency Fluctuations (ALFF) in the frontal cortex, parietal cortex, and putamen (Chen et al., 2020). LPE patients also showed significantly decreased short-range functional connectivity density in the bilateral middle temporal cortex, orbitofrontal cortex (OFC), thalamus, and nucleus accumbens (Lu et al., 2018). And LPE patients were reported to have increased functional connectivity (FC) between the amygdala and precuneus, posterior cingulate cortex (PCC), and middle temporal cortex, as well as decreased FC between the amygdala and precentral gyrus, insula, and inferior frontal cortex (Geng et al., 2021). Gao et al. (Gao et al., 2020) found that LPE patients had decreased hypothalamus-seeded FC related to the OFC, insula, superior temporal cortex, middle temporal cortex, fusiform, parahippocampus, and cerebellum. However, the precise relationship between altered brain function and the pathophysiology of LPE remains poorly understood.

Recently, the Percent Amplitude of Fluctuation (PerAF) method has been used in neuroimaging to investigate the neural mechanisms of certain diseases (Jia et al., 2020). PerAF is the percentage of blood oxygen level-dependent (BOLD) fluctuations relative to the mean BOLD signal intensity at each time point and averaged over the entire time series. As a recent voxel-level amplitude metric, it has been shown to be more reliable and sensitive than ALFF and fractional ALFF (fALFF) in a test-retest reliability analysis (Jia et al., 2020). But, to our knowledge, the PerAF approach has not been applied to explore LPE, which may be valuable in improving our understanding of LPE.

Advances in positron emission tomography (PET) and single photon emission computed tomography (SPECT) have made it possible to follow the pathways of neurotransmitters in the body. However, the use of radiolabeled tracers that bind specifically to certain neurotransmitters necessitates extensive experimentation to be feasible. The JuSpace toolbox, developed by Dukart et al., fills this gap. It considers changes in brain spatial patterns from MRI images from different groups and correlates these changes with the receptor/transporter protein maps included in the toolbox. This ultimately facilitates the linking of spatial patterns of observed brain changes in the target disease to the distribution of specific neurotransmitters (Dukart et al., 2021).

In this study, we therefore attempted to (i) investigate PerAF-altered brain regions in LPE patients compared to HCs, (ii) further explore the accuracy of predictions between LPE patients and HCs based on PerAF-altered brain regions by using receiver operating characteristic (ROC) curves, (iii) examine correlations between the neuroimaging findings and clinical characteristics in LPE patients, and (iv) investigate potential associations between PerAF alterations in LPE patients and specific neurotransmitter systems. We hypothesized that, compared to HCs, LPE patients would exhibit altered PerAF in specific brain regions involved in emotion, motivation, sensation, and inhibitory control processing. We also hypothesized that there might be significant correlations between the imaging alterations and clinical characteristics in LPE patients, and that PerAF alterations in LPE patients might be implicated in neurotransmitter dysregulation.

Materials and methods

Subjects

The study subjects consisted of 46 non-medicated LPE patients and 35 HCs. All subjects underwent a medical history assessment and physical examination. The inclusion and exclusion criteria for all participants were based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) definition and ISSM Guidelines (Althof et al., 2014; Battle, 2013), with detailed information provided in the Supplementary materials.

MRI data acquisition

The MRI imaging data were obtained from a 3.0T MRI system (Excite, General Electric) at a local hospital. The scan parameters of brain fMRI images were as follows: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, matrix size = 64 × 64, field of view (FOV) = 240 × 240 mm^2, slice thickness = 3.5 mm with no gaps, in-plane resolution = 3.75 × 3.75 mm^2, and 45 axial

slices. The scan parameters of T1 images were as follows: TR = 8.2 ms, TE = 3.2 ms, FA = 12°, data matrix = 256 × 256; FOV = 256 × 256 mm^2, in-plane resolution = 1 × 1 mm^2, slice thickness = 1.0 mm. Head movement was restricted using foam padding during the resting scanning, and all subjects were instructed to lie still without engaging in any specific thoughts.

MRI data preprocessing

In this study, the preprocessing of the fMRI data was conducted using the Data Processing & Analysis for Brain Imaging (DPABI 6.2; http://rfmri.org/dpabi) toolbox, which is based on Statistical Parametric Mapping 12 (SPM12, UK, http://www.fil.ion.ucl.ac.uk/spm) and implemented on the MATLAB platform. Further details are provided in the Supplementary materials.

PerAF analysis

The PerAF of each voxel was estimated using the following equations:

$$PerAF = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{X_i-\mu}{\mu}\right| \times 100\%$$

$$\mu = \frac{1}{n}\sum_{i=1}^{n} X_i$$

Here, "X" indicates the signal intensity at a time point, "n" indicates the total number of time points in the time course, and "μ" refers to the average value of the time course.

Statistical analysis

The demographic and clinical data were analyzed using SPSS, Version 22.0 (IBM, Armonk, New York), with a significance level set at $p < 0.05$. A two-sample t-test was conducted to investigate PerAF-related imaging differences between LPE patients and HCs, with significance determined at $p < 0.05$, corrected for false discovery rate (FDR). Brain regions exhibiting group differences in PerAF were further evaluated using ROC curve, with statistical significance determined through nonparametric permutation testing (10,000 permutations). The significance threshold was set at $p < 0.05$.

Pearson's correlation analysis was then used to examine the possible relationships between the imaging alterations and clinical characteristics in LPE patients, with the significant threshold set at $p < 0.05$ (Bonferroni corrected).

Neurotransmitter correlates of abnormal PerAF in LPE

The JuSpace toolkit (version 1.4; https://github.com/juryxy/JuSpace) was employed to investigate potential associations between PerAF alterations in LPE patients compared to HCs and specific neurotransmitter systems (Dukart et al., 2021). We focused on evaluating the serotonin, dopamine, GABA, and glutamate systems, with consideration given to the following neurotransmitter components: serotonin 1a (5-HT1a) receptor, 5-HT2a receptor, serotonin transporter (SERT), D1 receptor, D2 receptor, dopamine transporter (DAT), fluorodopa F18 (FDOPA), GABAa receptor, vesicular acetylcholine transporter (VAChT), metabotropic glutamate receptor 5 (mGLUR5), and norepinephrine transporter (NAT).

For each extracted neurotransmitter distribution map, its Spearman's rank correlation with PerAF alterations in LPE patients was computed (based on the Neuromorphometrics Atlas; exact p values; $N = 1000$ permutations; adjusted for spatial autocorrelation).

Results

Demographics and clinical characteristics result

The key demographic and clinical characteristics of LPE patients and HCs are presented in Table 1. There were no significant statistical differences in the age or International Index of Erectile Function scores (IIEF-5 scores) between LPE patients and HCs ($p > 0.05$). LPE patients had significant differences in the Premature Ejaculation Diagnostic Tool (PEDT), Intravaginal Ejaculatory Latency Time (IELT), Self-rating Anxiety Scale (SAS), and Self-rating Depression Scale (SDS) compared to HCs.

Table 1 Demographic and clinical characteristics for LPE patients and HCs

Characteristics	Mean ± SD		*P* Value
	LPE ($n = 46$)	HCs ($n = 35$)	
Age (years)	30.33 ± 5.16	31.66 ± 3.02	0.178
IIEF-5 Score	23.85 ± 0.84	24.26 ± 1.24	0.082
IELT (seconds)	39.74 ± 14.62	652.29 ± 327.94	< 0.001
PEDT	17.15 ± 1.87	0.91 ± 1.54	< 0.001
SAS	38.70 ± 5.96	30.34 ± 1.71	< 0.001
SDS	40.85 ± 3.41	30.29 ± 2.07	< 0.001

SD standard deviation, *LPE* lifelong premature ejaculation, *HCs* healthy controls, *IIEF* International Index of Erectile Function, *IELT* Intravaginal Ejaculatory Latency Time, *PEDT* Premature Ejaculation Diagnostic Tool, *SAS* Self-rating Anxiety Scale, *SDS* Self-rating Depression Scale. *P* values were obtained by two-sample two-tailed t-test

Imaging results

The significant differences in PerAF between LPE patients and HCs are illustrated in Figs. 1, S1 and Table S1. Compared to HCs, LPE patients had increased PerAF in the right middle cingulate cortex (MCC), left supramarginal gyrus (SMG), right Rolandic operculum, right parahippocampus/hippocampus (ParaHIPP/HIPP), left insula, along with decreased PerAF in the left precuneus, right inferior temporal cortex (ITC), left calcarine, and right cuneus.

The ROC analysis revealed discrimination performance with an AUC of 0.77 for the right MCC, 0.74 for the left SMG, 0.79 for the right ParaHIPP/HIPP, 0.74 for the right ITC, and 0.76 for the right cuneus ($p < 0.001$). Additionally, the AUC was 0.73 for the left insula, 0.73 for the left precuneus ($p = 0.001$), 0.69 for the right Rolandic operculum, and 0.676 for the left calcarine ($p = 0.003$) (Fig. 2). The ROC analysis results of three methods, ALFF, fALFF, and PerAF, were compared to assess the utility of PerAF. (Table S2)

Furthermore, in LPE patients, there was a positive correlation between increased PerAF in the insula and depression score ($r = 0.349$, $p = 0.017$), as well as a positive correlation between decreased PerAF in the precuneus and the lower IIEF score ($r = -0.35$, $p = 0.017$) in LPE patients (Fig. 3).

Spatial correlation of abnormal PerAF with neurotransmitter distribution

Individual PerAF alterations in LPE patients as compared to HCs were significantly associated with the spatial distribution of D2 ($r = 0.117$, $p = 0.04$), DAT ($r = 0.143$, $p = 0.002$), SERT ($r = 0.093$, $p = 0.017$), VAChT ($r = 0.211$, $p = 0.001$), and NAT ($r = 0.162$, $p = 0.001$) in LPE patients. (Fig. 4).

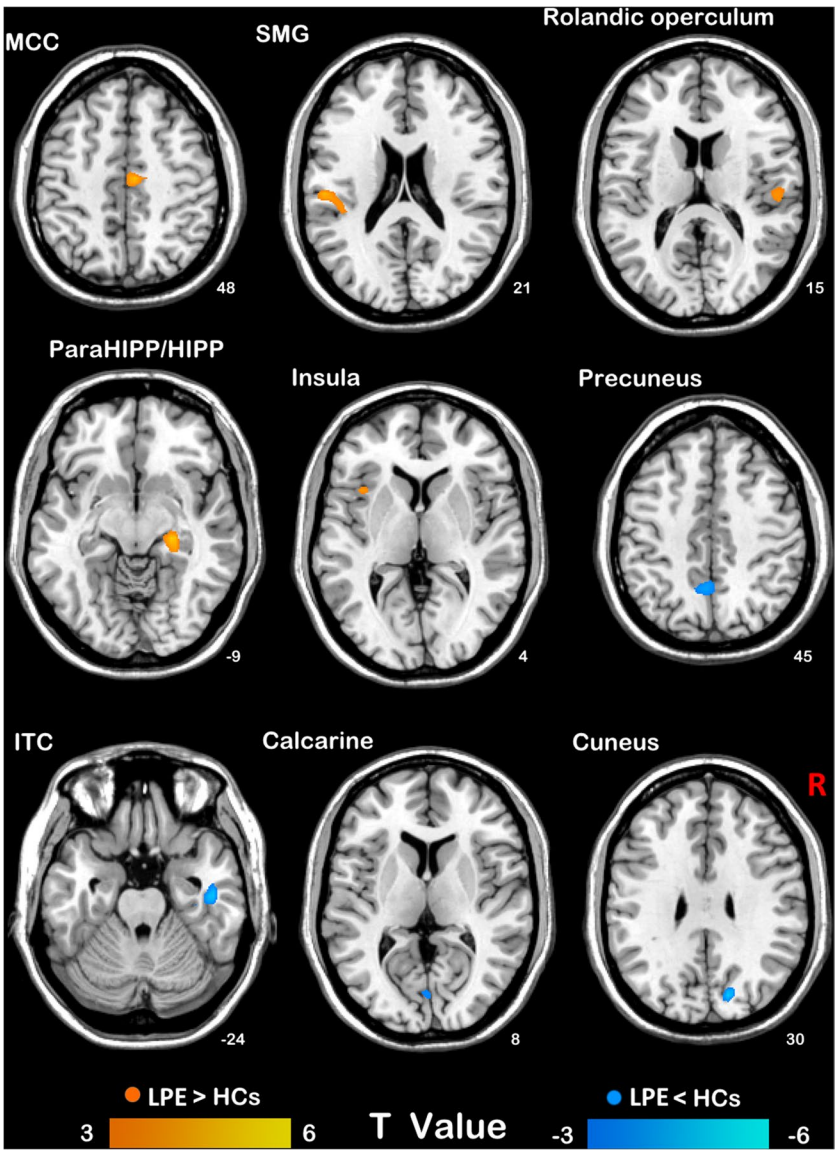


Fig. 1 Brain regions showing significant PerAF differences between LPE patients and HCs. Abbreviations: PerAF, percent amplitude of fluctuation; LPE, lifelong premature ejaculation; HCs, healthy controls; MCC, middle cingulate; SMG, supramarginal gyrus; ParaHIPP/HIPP, parahippocampus/hippocampus; ITC, inferior temporal cortex; R, right

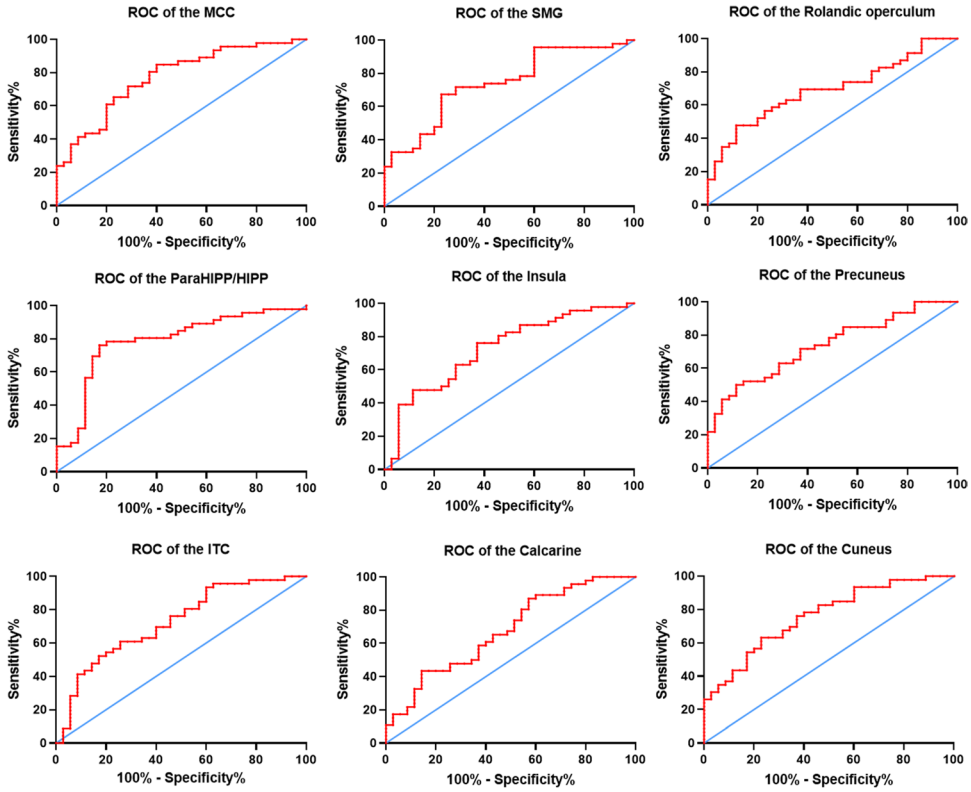


Fig. 2 ROC curves for the brain regions showing PerAF-related group differences. Abbreviations: ROC, receiver operating characteristic; PerAF, percent amplitude of fluctuation; MCC, middle cingulate cortex; SMG, supramarginal gyrus; ParaHIPP/HIPP, parahippocampus/hippocampus; ITC, inferior temporal cortex; LPE, lifelong premature ejaculation; HCs, healthy controls

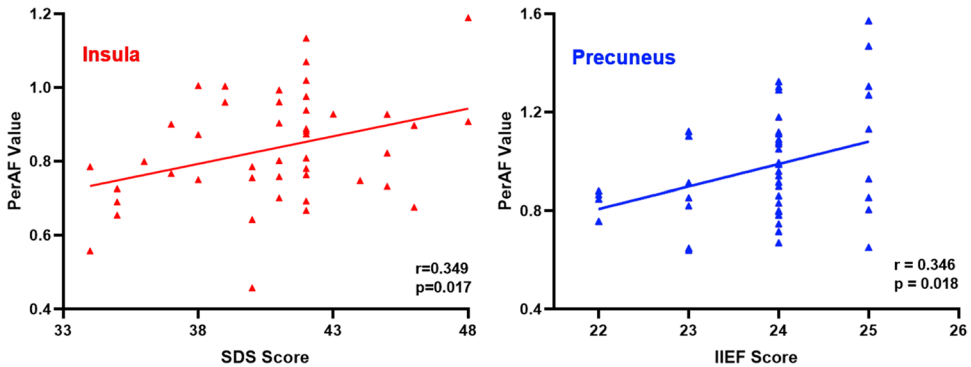


Fig. 3 Correlations between the PerAF in the insula and the PEDT score and between the IIEF-5 score and PerAF in the precuneus in LPE patients. Abbreviations: PerAF, Percent Amplitude of Fluctuation; PEDT, Premature Ejaculation Diagnostic Tool; IIEF, International Index of Erectile Function; LPE, lifelong premature ejaculation

Discussion

In this study, we used the PerAF analysis method to investigate alterations in resting-state brain functions in LPE patients compared to HCs. A comparison was performed to validate the usefulness of PerAF, and we found increased PerAF in the MCC, SMG, Rolandic operculum, ParaHIPP/HIPP, and insula, as well as decreased PerAF in the precuneus, ITC, calcarine, and cuneus. The MCC and ParaHIPP/HIPP presented higher classification power than other brain regions. There were positive correlations between the SDS score and PerAF in the insula and between the IIEF score and PerAF in the precuneus. Altered PerAF in LPE patients were significantly associated with the spatial distribution of the neurotransmitters D2, DAT, SERT, NAT, and VAChT.

Abnormal PerAF in LPE patients

We found increased PerAF in the MCC and SMG in LPE patients compared to HCs in this study. The MCC is well known to be involved in the processing of complex tasks such as cognition, anxiety, motor, and pain. As a pivotal component of the homeostatic afferent network and the emotional-arousal network, the MCC has been implicated in assessing the importance of visceral stimulation and emotional regulation (Di Cesare et al., 2021). MCC-related

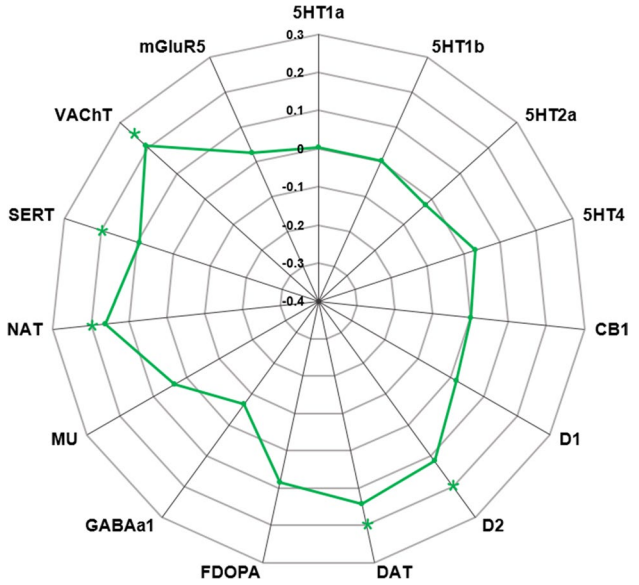


Fig. 4 Correlation between PerAF alterations in LPE patients and neurotransmitters spatial distribution. PerAF alterations in LPE patients as compared to HCs were significantly associated with spatial distribution of D2, DAT, SERT, VAChT and NAT in LPE patients. Abbreviations: PerAF, Percent Amplitude of Fluctuation; LPE, lifelong premature ejaculation

dysfunction was found in the LPE patients. And the MCC exhibited better classification power in differentiating the LPE patients from HCs in our study. The SMG belongs to the somatosensory association cortex and is related to the detection of voluntary movement (Goble et al., 2012). And Guo et al. (Guo et al., 2018) found the significantly increased thickness of the SMG in PE patients. Taken together, we speculate that the increased PerAF in the MCC and SMG may be associated with abnormal regulation of sensory or emotional information.

Compared to HCs, LPE patients were found to have decreased PerAF in the precuneus within the default mode network (DMN) in this study. Accumulating neuroimaging studies have shown that the DMN is a crucial intrinsic brain network (Smallwood et al., 2021; Yeshurun et al., 2021). As another important region within the DMN, the precuneus is found to be associated with visuo-spatial imagery, episodic memory retrieval, self-related processing, and aspects of consciousness (Cavanna & Trimble, 2006). Previous studies have reported brain regional dysfunction (such as visual processing, emotion regulation, and motor execution) within the DMN following visual stimulation in LPE patients (Li et al., 2019; Whitfield-Gabrieli & Ford, 2012). Thus, our study may provide further evidence to support that the abnormal DMN may be involved in the central mechanism underlying LPE and may lead to dysregulation of emotional and somatosensory processing in LPE patients.

Increased PerAF in the insula was found in LPE patients compared to HCs in our study. The insula has been extensively investigated in the male reproduction field, mainly in relation to erectile consciousness and feeling penis stimulation (Arnow et al., 2002). It has been reported that sexual stimulation induces activation in the insula in healthy men (Cera et al., 2020). And several PE studies have also indicated abnormal changes in insula functions (Gao et al., 2022). Therefore, it can be speculated that our insula-related result is involved in the altered mediation of erection in LPE patients.

We found that LPE patients showed increased PerAF in the ParaHIPP/HIPP compared to HCs in our study. ParaHIPP/HIPP is well known to be related to memory, but it is also associated with emotional processing. Compared to HCs, LPE patients were reported to have decreased 19–21 Hz band current source density in the ParaHIPP during audiovisual erotic stimuli and decreased functional connectivity between the ParaHIPP and the hypothalamus (Hyun et al., 2008). We speculate that increased PerAF in the ParaHIPP/HIPP may be implicated in changed emotion processing and/or changed memory information processing of unsatisfactory sexual experiences in LPE patients.

In this study, LPE patients had increased PerAF in the Rolandic operculum compared to HCs. The Rolandic operculum was reported to be associated with emotional processing, including depression and anxiety (Koelsch et al., 2006; Maria et al., 2022). In this study, LPE patients had the higher SAS and SDS than HCs, which was similar to the results from other PE studies. Recently, the Rolandic operculum has also been identified as being associated with visceral sensation. And the gastrointestinal tract could be sensitive to emotional depression, anxiety, and stress. Therefore, the increased PerAF in the Rolandic operculum may reflect an abnormality in emotional processing in LPE patients and may contribute to the sensory processing of rapid ejaculation.

In addition, we found decreased PerAF in the occipital cortex compared to HCs. The occipital cortex is associated with sensory processing of auditory-spatial and visuospatial information. The anxious response and self-regulatory dysfunction may induce activation in the occipital cortex in anxious patients (Thorsen et al., 2019). As a part of the visual association cortex, a previous study revealed that occipital cortex hyperconnectivity is implicated in the abnormal integration of visual information and elevated sensitivity to visual erotic stimuli in LPE patients (Guo et al., 2018). Moreover, sexual responses are elicited by external stimuli such as visual input and internal stimuli, independent of any sexual psychological stimulation (Waberski et al., 2008). The present findings may suggest that changes in ejaculation-related vision, sensation, and emotion may be related to the abnormal responses in the occipital cortex. However,

the specific role of the occipital cortex in LPE patients may require investigation.

PerAF alterations in LPE patients are associated with neurotransmitter profiles

Neurotransmitter research in PE has been widely discussed. This study revealed that the abnormalities in imaging characteristics in LPE patients were associated with dysregulation in the neurotransmitter systems of dopamine, serotonin, and norepinephrine. Dopamine receptors, which bind to G-proteins, are intricately interwoven with various aspects of voluntary movement, reward processing, and emotional regulation in humans (Beaulieu & Gainetdinov, 2011). Increased serotonin was linked to prolonged ejaculation latency (Clement & Giuliano, 2016), while norepinephrine could inhibit the contraction of the human seminal vesicle (Gajar et al., 2007). Additionally, the abnormal activation of Vacht has been implicated in the imbalance of acetylcholine levels in the central nervous system. This imbalance led to excessive neural excitation during the ejaculation process and a decrease in the ability to control the penile muscles (Chen et al., 2021). Recently, it is noteworthy that the excessive pleasure experienced by PE patients during sexual activity, which indicates dysregulation of reward processing, exceeds their cognitive control and is considered a core mechanism in the etiology of PE (Li et al., 2023). Ozdemir (Ozdemir, 2012) hypothesized that PE was an impulse control disorder because it shared dysregulation of the same neurotransmitter systems (dopaminergic, serotonergic, and noradrenergic systems) that were implicated in impulse control disorders. Our findings provide potential evidence for the feasibility of this hypothesis. Ayribas and Toprak (Ayribas & Toprak, 2021) found that PE patients may suffer from severe social cognitive impairment and anxiety. Draps et al. (Draps et al., 2020) observed minimal differences in gray matter volume between impulse control and addiction disorders, suggesting similarities between impulse control and addiction. Recent research also suggests an association between self-perceived sexual addiction and sexual dysfunction (Whelan & Brown, 2021). The relationship between altered neurotransmitter systems, abnormal cognitive controlling (e.g., impulse control disorder), and addiction in LPE patients deserves further investigation.

Several limitations of our research should be mentioned. Firstly, this is a cross-sectional study, and the sample size in our research is relatively small. Larger imaging datasets should be collected to draw more definitive conclusions in the future. Secondly, we only assessed the abnormalities of brain function, future investigations should combine other imaging modalities with fMRI. Multimodal fusion is getting increasing attention in imaging research, as it may provide more meaningful results and conclusions.

Conclusions

In conclusion, the present imaging findings indicate that LPE patients have changed PerAF in the MCC, SMG, Rolandic operculum, ParaHIPP/HIPP, insula, precuneus, ITC, calacrine and cuneus, which are implicated in altered emotional processing, sensory processing, and visual processing of rapid ejaculation. Meanwhile, we tentatively suppose that the combined dysregulation of four neurotransmitter systems observed in LPE patients may be associated with the abnormal control of ejaculatory function. The current imaging findings may provide evidence that brain dysfunction is involved in LPE. We hope that our study will further our understanding of the pathophysiology of LPE.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11682-024-00920-8.

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Author contributions Ming Gao was responsible for the study concept and design as well as drafted the manuscript; Pinxiao Wang, Jiarui Yuan and Dingxin Nie assisted with data analysis and interpretation of findings and drafted the manuscript; Wanxiang Zheng, Kepu Liu, Jianyong Feng, Yuntao Zhang, Yanzhu Wang and Junjun Gao contributed to acquisition of MRI data and study design; Dingxin Nie contributed to data analysis and interpretation of findings. All authors critically reviewed the content and approved the final version for publication.

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Data availability The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethics statement The procedures of the study were approved by the Ethical Committee of the local hospital and were conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Each subject signed a written informed consent before study participation.

Consent to participate All participants volunteered to participate in the present study with informed consents.

Consent to publish All the authors agreed to publish this study in this journal.

Competing interests The authors declare no competing interests.

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