EJACULATION DISORDERS

Changes in the Amplitude of Low-Frequency Fluctuation in Patients With Lifelong Premature Ejaculation by Resting-State Functional MRI

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ABSTRACT

Introduction: Dapoxetine is considered a first-line treatment for patients with lifelong premature ejaculation (PE), and current researches have showed with functional magnetic resonance imaging (fMRI) that patients with lifelong PE might have abnormal brain function, but differences in brain function before and after administration have not been reported.

Aim: The aim of this study was to determine some objective differences in brain function between patients with lifelong PE before and after administration and healthy individuals.

Methods: In this study, 17 patients with lifelong PE and 11 healthy controls underwent clinical assessments and resting-state fMRI examination. After 4 weeks of treatment with dapoxetine 30 mg as needed, patients with PE underwent the same fMRI examination again 3 hours after dapoxetine administration.

Main Outcome Measure: The data were preprocessed using a data processing assistant for resting-state fMRI, and voxelwise amplitude of low-frequency fluctuation (ALFF) maps was calculated to identify abnormal neural activity in the brain.

Results: (a) The ALFF of patients with PE was significantly lower in the bilateral hippocampus and thalamus and higher in the left fusiform and lingual gyrus than that of healthy controls; (b) decreased and increased ALFF in patients with PE recovered after dapoxetine administration.

Conclusion: We preliminarily identified the relevant sites by analyzing changes in the ALFF in patients with lifelong PE. Analyzing ALFF changes in the brain by resting-state fMRI is an effective method to study PE, and it might provide a reference for disease diagnosis and future research. **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;9:100287**

Key Words: Lifelong Premature Ejaculation; Healthy Control; Dapoxetine; Amplitude of Low-frequency Fluctuation

INTRODUCTION

Premature ejaculation (PE) is a common male sexual dysfunction that has substantial negative personal and interpersonal psychological consequences[1] with an approximately 5% prevalence in general populations.[2] Although the etiology and pathophysiology of PE have not been well elucidated, PE is defined by the International Society for Sexual Medicine as a lifelong and acquired disease, and 2 new subtypes in addition to the pre-existing lifelong and acquired PE subtypes have been added: variable PE and subjective PE.[3] Studies have demonstrated that PE is associated with the dysfunction of 5-hydroxytryptamine (5-HT) and 5-HT receptors, and the former is a neurotransmitter related to the excitability of the ejaculation center in the brain[4] and is the most important central neurotransmitter involved in delaying ejaculation.[5] The use of selective serotonin reuptake inhibitors in the treatment of PE is widely recognized.[6] As a short-acting selective serotonin reuptake inhibitor, dapoxetine is considered a first-line treatment for

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patients with lifelong PE,[7] but some patients do not achieve a satisfactory result in our clinical experience.

Current research and clinical results showed with functional magnetic resonance imaging (fMRI) that some patients with lifelong PE might have abnormal brain function.[8–10] Blood oxygen level–dependent (BOLD) fMRI is a promising technique to quantitatively and noninvasively probe functional brain activities. The amplitude of low-frequency fluctuation (ALFF) is a resting-state fMRI indicator that measures the spontaneous neural activity of the BOLD signal and has been used to identify abnormal regional brain activity in a wide range of brain diseases.[11]

In this study, we performed resting-state fMRI examinations on patients with lifelong PE before and after dapoxetine administration and healthy controls without any medication. And we hypothesized that there might be some objective differences in brain function between patients with lifelong PE and healthy individuals. Knowing and mastering these differences would help physicians in the diagnosis and treatment of lifelong PE.

MATERIALS AND METHODS

Subjects

There were 17 patients with lifelong PE and 11 healthy male control volunteers. Patients were recruited from urologic surgery clinic in our hospital and controls were recruited from the physical examination center through publicly posting posters. Patients with PE were included based on the following criteria: (a) PE diagnosis in accordance with the International Society for Sexual Medicine definition that ejaculation always or nearly always occurs before or within approximately 1 minute of vaginal penetration[12]; (b) premature ejaculation diagnostic tool (PEDT) score $\geq$11; and (c) self-report of uncontrollable ejaculation and negative personal consequences, such as frustration and avoidance of sexual intimacy. Healthy controls were included if they had good sexual satisfaction with their partners and their intravaginal ejaculation latency time (IELT) was $\geq$3 minutes. Individuals were excluded if they met any of the following exclusion criteria: (a) diagnosis of erectile dysfunction (ED); (b) dependency on drugs or alcohol; (c) a medical history of cardiovascular disease, diabetes mellitus, mental disease, trauma, or other disorder; (d) contraindications to MRI; or (e) poor patient compliance. Individuals who had morphological changes in their brain, such as intracranial arachnoidal cysts, were excluded because of the effects on image analysis. Patients who were not willing to take dapoxetine were excluded as well. Meanwhile, all the potential subjects were screened at first by taking medical history, reviewing of medical records, and performing physical exams to exclude those with medical problems potentially affecting the central nervous system such as schizophrenia. This study was approved by the Ethical Committee of the Second Affiliated Hospital of Xi'an Jiao Tong University, and the written informed consent was obtained from all subjects.

Examinations

Clinical Assessments

Both groups reported their medical history, underwent physical examination, completed the PEDT, and had their hormone levels measured. A total PEDT score of $\geq$11 suggested a diagnosis of PE; a score of 9 and 10 indicated probable PE; and a score $\leq$8 indicated no PE.[13] Individuals were excluded if they had the following PEDT scores: <11 for patients with PE and >8 for controls. The purpose of the physical examination was mainly to exclude individuals with genital abnormalities. To measure the hormone levels, fasting blood samples were drawn between 8:00 and 8:30 AM.

MRI Examination

Healthy controls and patients with PE underwent fMRI examination when the clinical assessments were completed. 4 weeks later, patients with PE underwent the same fMRI examination again 3 hours after administration of dapoxetine 30 mg. In this 4-week period, patients with PE were required to have sex at least 6 times with treatment of dapoxetine 30 mg as needed. The patients completed the PEDT again after a second fMRI examination. The process of this research is shown in Figure 1.

MRI Data Acquisition

Preparation Before the Examination

All participants were instructed to stay awake with their eyes closed. In the supine position, head movement was restricted using sponge padding. Earplugs were used to reduce the noise of the machine for subjects.

Imaging Equipment and Parameters

The MRI data were acquired with a Signa HDXT 3.0 T MR scanner (GE, Milwaukee, WI, USA). High-resolution T1 structural images were acquired for structural reference. The parameters for T1 imaging were as follows: repetition time = 1900 ms; echo time = 2.5 ms; field of view = 250 mm × 250 mm; flip angle = 9°; slice thickness = 1.0 mm; slice interval = 0.5 mm; and number of slices = 176. The resting-state fMRI data were acquired using a gradient echo planar imaging sequence with repetition time = 2000 ms; echo time = 30 ms; field of view = 250 mm × 250 mm; flip angle = 90°; slice thickness = 3.5 mm; slice interval = 1 mm; and number of slices = 31.

Data Preprocessing and Analyses

The data were preprocessed using data processing assistant for resting-state fMRI (DPARSF) (http://rfmri.org/DPARSF). The first 10 volumes of each fMRI sequence were removed. The remaining sequence was corrected for motion and slice timing, followed by normalization to a 3-mm MNI template, spatial

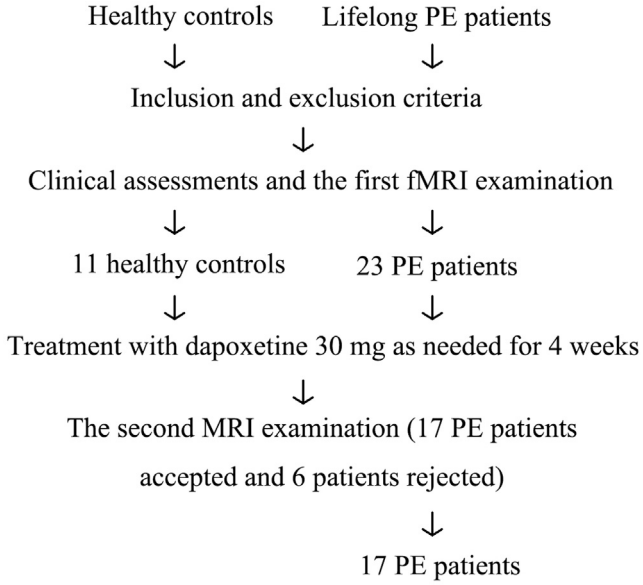

Figure 1. The research process.

smoothing using a Gaussian filter with a 6-mm full width at half maximum, linear trend removal, and temporal filtering (0.01 Hz < f < 0.08 Hz). After preprocessing, DPARSF was used to calculate a voxelwise ALFF map for each sequence.

Statistical Analyses

The collected data were analyzed using IBM SPSS Statistics, version 18.0 (IBM, Armonk, NY, USA). Quantitative variables were expressed as the mean ± standard deviation. Independent samples T-tests were used to compare the ages, body mass indexes, IELTs, PEDT scores, and sexual hormone, and blood glucose levels between the 2 groups. It was also performed to identify brain regions with significantly altered neural activity between healthy controls and patients with PE before and after treatment (false discovery rate—corrected, cluster size >10 voxels). A paired-sample T-test was performed to identify those in patients with PE before and after treatment (false discovery rate—corrected, cluster size >10 voxels). Statistical significance was defined as $P < .05$.

RESULTS

Subject Characteristics

The demographics and results of clinical examinations are summarized in Table 1. Positive results ($P < .05$) were obtained for the IELT, PEDT score, and free testosterone (FT) level between the 17 patients with PE and the 11 healthy controls. A significant reduction in PEDT scores was also observed after the 4-week treatment with dapoxetine in the 17 patients with lifelong PE compared with before treatment ($P < .05$).

fMRI Analyses

Brain regions were regarded as responsive to medication under 2 conditions: (a) decreased ALFF measures in patients compared with healthy controls and increased ALFF measures after medication and (b) increased ALFF measures in patients compared with healthy controls and decreased ALFF measures after medication. And there is no significant difference on ALFF between the healthy controls and the patients with lifelong PE after medication. Decreased neural activity in patients with PE recovered after dapoxetine treatment in the bilateral hippocampus and bilateral thalamus (Figure 2A—D). Increased neural activity in patients with PE recovered after dapoxetine treatment in the left fusiform gyrus and lingual gyrus (Figure 2E—F). Detailed coordinates of these brain regions are summarized in Table 2.

DISCUSSION

In accordance with the European Association of Urology Guidelines 2020, the diagnosis and classification of PE is mainly based on medical and sexual history, and laboratory or

Table 1. Demographics and results of clinical examinations in the PE and control groups

Characteristics	PE group (n = 17)	Control group (n = 11)	T Values	*P* Values
Age (years)	30.88 ± 4.66	31.36 ± 3.64	−0.289	.775
BMI	22.98 ± 2.65	24.34 ± 3.21	−1.221	.233
IELT (minutes)	1.62 ± 0.60	7.09 ± 4.95	−3.651	.004
PEDT score	13.41 ± 2.03	5.82 ± 2.09	9.551	$P < .001$
GLU (mmol/L)	5.40 ± 0.46	5.28 ± 0.89	0.472	.641
E_2 (pg/ml)	25.89 ± 7.27	27.22 ± 6.19	−0.503	.619
TT (ng/dl)	549.10 ± 200.60	429.81 ± 139.13	1.718	.098
FT (pg/ml)	28.03 ± 8.07	16.93 ± 5.48	3.991	$P < .001$
LH (mIU/ml)	4.97 ± 1.96	4.50 ± 2.74	0.527	.603
FSH (mIU/ml)	3.99 ± 1.85	4.45 ± 2.04	−0.615	.544
PROG (ng/ml)	0.24 ± 0.11	0.22 ± 0.14	0.368	.716
PRL (ng/ml)	12.52 ± 5.14	12.24 ± 5.06	0.142	.889

BMI = body mass index; IELT = intravaginal ejaculation latency time; PEDT = premature ejaculation diagnostic tool; GLU = glucose; E_2 = estradiol; TT = total testosterone; FT = free testosterone; LH = luteinizing hormone; FSH = follicle stimulating hormone; PROG = progesterone; PRL = prolactin; PE = premature ejaculation.

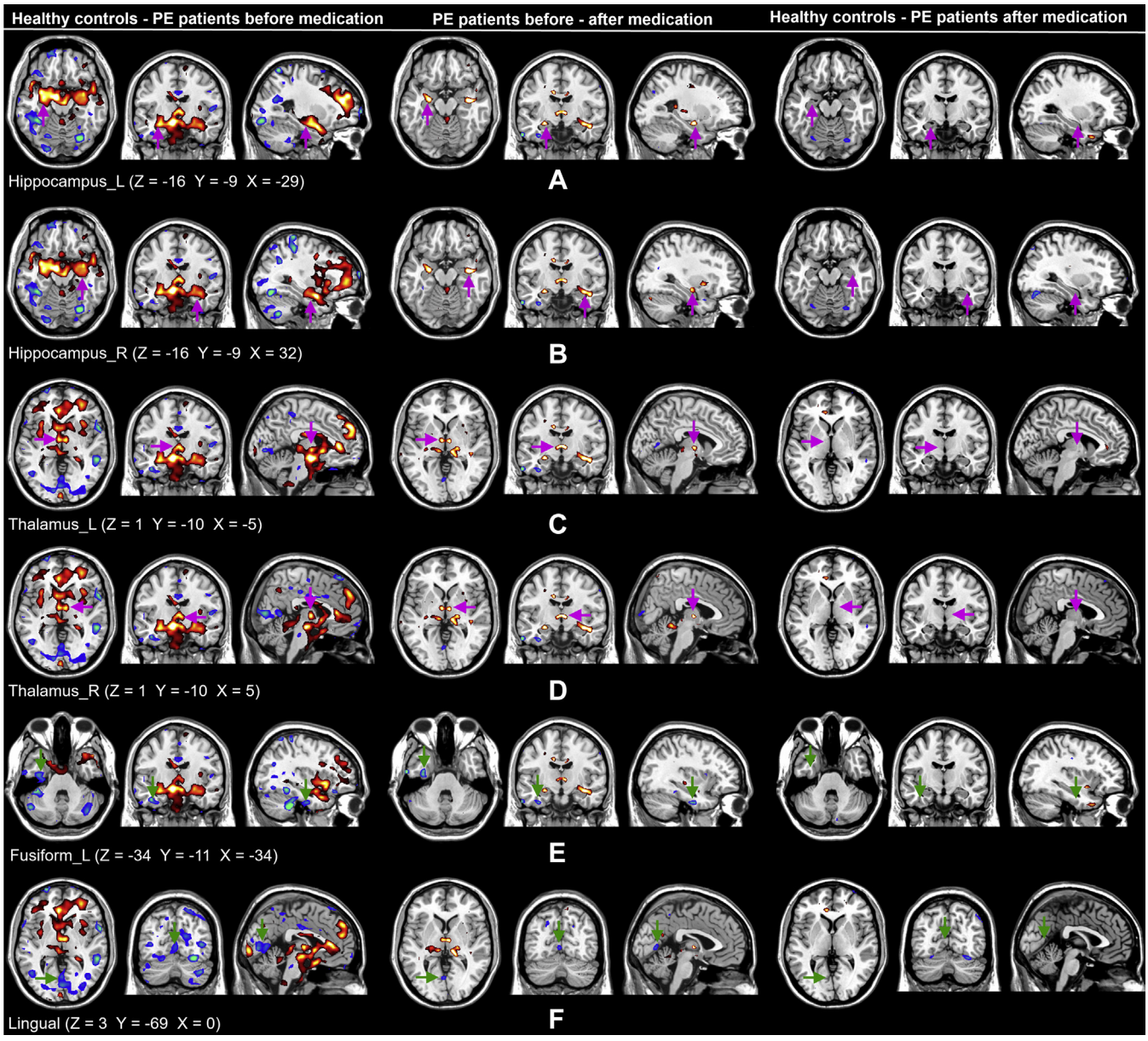

Figure 2. Brain regions that responded to dapoxetine in patients with lifelong PE. (A-D) show that decreased neural activity in the bilateral hippocampus and bilateral thalamus recovered in patients with lifelong PE after medication. (E, F) show that increased neural activity in the left fusiform gyrus and lingual gyrus recovered in patients with lifelong PE after medication. PE = premature ejaculation.

physiological testing is not routinely recommended, which introduces many confounding factors because of the lack of accurate and objective measures. Consequently, the diagnosis of PE has always lacked an effective and objective indicator, and there remains much uncertainty about lifelong PE. For instance, the IELT of one person with prostatitis might be less than 1 minute during the first time of sexual intercourse, and afterward, the IELT may be persistently short due to prostate or other factors. This type of patient should be diagnosed with acquired PE, but he is likely to be diagnosed with lifelong PE if only the medical history and chief complaint are considered. In addition, some lifelong PE may result from penile hypersensitivity[14] or psychological and relational problems.[15] These situations could explain why dapoxetine is ineffective for some patients with so-called lifelong PE, as their PE is not related to 5-HT. Finding an objective diagnostic tool can help screen in advance and accurately diagnose PE.

In our study, 23 patients with lifelong PE were initially included based on their PEDT scores and other criteria, but only 17 underwent 2 fMRI examinations. 6 patients rejected the second fMRI because dapoxetine was ineffective for them. The remaining 17 patients underwent the second fMRI, as dapoxetine had obviously increased their IELT. Therefore, we only targeted patients with lifelong PE who had positive results with dapoxetine, and we failed to collect data on the differences in the ALFF between dapoxetine-sensitive and dapoxetine-resistant

Table 2. The coordinates of brain regions that responded to dapoxetine in patients with lifelong PE

Sites	Data for coordinates	Name of individual voxel
(a)	(−29, −9, −16)	Hippocampus-L
(b)	(32, -9, −16)	Hippocampus-R
(c)	(−5, -10, 1)	Thalamus-L
(d)	(5, −10, 1)	Thalamus-R
(e)	(−34, −11, −34)	Fusiform gyrus-L
(f)	(0, −69, 3)	Lingual gyrus

PE = premature ejaculation.

patients. Although the 6 patients we failed to follow-up indirectly helped us identify dapoxetine-sensitive patients with lifelong PE, more clinical studies on these patients are required in future research. In addition, these results showed that etiologic differences in lifelong PE might still exist as per the current diagnosis tool.[14,15]

Considering medical ethics and the low operability in clinical practice, it is difficult to perform task-state fMRI on patients with PE, whereas resting-state fMRI, which has been used in a variety of diseases, such as mild cognitive impairment,[16] epilepsy,[17] and hepatic encephalopathy,[18] is particularly suitable. Yang reported that patients with PE have an abnormal brain control network, which may contribute to the reduced central control of rapid ejaculation.[8] Zhang suggested that the brain activity in the left inferior frontal gyrus and left insula decreased and activation in the right middle temporal gyrus increased during the task.[9] These findings revealed that brain function in certain areas is affected in cases of lifelong PE. Interestingly, our results showed decreased ALFF in the bilateral hippocampus and thalamus and increased ALFF in the left fusiform and lingual gyrus, which recovered after treatment with dapoxetine 30 mg in patients with lifelong PE. That is to say, we identified dapoxetine-sensitive patients with lifelong PE by using the ALFF in fMRI, and it might be an approach to screen suitable patients who would response effectively to dapoxetine, which makes our clinical diagnosis more comfortable for the patient and accurate compared with a self-reported sexual history.

A previous study suggested that the hippocampus contributes to episodic, spatial, and semantic aspects of memory and is sensitive to temporal durations within sequences of events and intervals.[19] The thalamus, which plays a central role in cognitive, sensory, and emotional information processing, is involved in several diseases, such as depressive disorder.[20] Brain imaging studies have shown that the fusiform gyrus is involved in language comprehension and facial recognition,[21] and the left lingual gyrus is associated with the relevant visual imagery,[22] while the right lingual gyrus is related to predictive inference generation.[23] Papez circuit is a neural loop including the hippocampus, mammillary bodies, anterior thalamic nuclei, and posterior cingulate region, which is critical for the consolidation of declarative memory.[24] Cingulate gyrus is mainly made up of 3 divisions: anterior for emotion, middle for pain cognition and response selection, and posterior/retrosplenial cortices for spatial information processing and long-term memory formation.[25,26] Although not all of the regions found in our study were included in Papez circuit or cingulate gyrus, the results still suggested that there is some correlation between PE and emotion. A study has reported that hippocampal abnormalities on structure and function are found in many disorders. For example, hippocampal volume loss is associated with depression.[27] Consequently, considering the probable association of the sites we identified with other mental disease such as depression, it is not clear whether this finding is due to the emotional problems caused by PE or the personality characteristics of the patients themselves. But surely all the subjects showed no symptoms involved in psychosis during the study period, and there were no medical history or medical records about psychosis as well. We tried to ensure the homogeneity of the subjects as far as possible. Undoubtedly, a larger sample size and a more optimal experimental design are required to determine a causal relationship.

The advantages of BOLD fMRI are its noninvasive nature, increasing availability, relatively high spatiotemporal resolution, and capacity to demonstrate the entire network of areas.[28] One of the advantages of fMRI in clinical practice is that it can reflect functional changes in the subclinical stage of the disease before structural changes. Therefore, this technology would also be expected to be used for early screening of patients with PE and brain functional imaging changes, which helps timely intervention and the ability to obtain an ideal therapeutic effect. At present, there is insufficient evidence to support this point, and prospective clinical studies with independent evaluation for this method are needed. What is noteworthy is that resting-state fMRI in recent years has been widely used to assess functional brain alterations and establish imaging biomarkers in a wide range of neurological and mental diseases. Meanwhile, there are many methods for data postprocessing and analyzing, such as seed-based correlation analysis,[29] independent component analysis,[30] ALFF,[31] and regional homogeneity.[32] The ALFF is computationally efficient, straightforward, and easy to interpret. Thus, it may serve as a potential imaging biomarker for the diagnosis and treatment monitoring of patients with PE. However, as a univariate approach, the ALFF inherently ignores functional interactions among spatially distributed large-scale brain regions. In the future, it would be interesting to explore brain network-level biomarkers for PE by adopting a wide range of functional brain network analytical pipelines.

The need to objectively evaluate PE has led to the development of several questionnaires, and the most widely used tools include the PEDT and Arabic Index of Premature Ejaculation. Several studies have demonstrated the reliability and validity of the PEDT,[33] and we also found a significant difference in the PEDT scores between patients with PE and healthy controls in this study, which indicated the clarity of grouping. The

significant reduction in the PEDT scores of patients with lifelong PE suggested that dapoxetine was effective in these patients. Several studies have reported that PE and ED would be co-existence in a way,[34] so we used erectile hardness score to avoid the effect of ED on this research, which meant subjects whose erectile hardness score were below grade 3 were excluded when performing exclusion criteria. Previous research has shown that patients with PE have higher FT than normal men who have no sexual dysfunction.[35] Keleta et al[36] demonstrated that chronic treatment with testosterone in rats significantly reduced the level of 5-HT in the brain. In our study, the level of FT in patients with PE was significantly higher, and we speculated that high FT might be a major cause of facilitating ejaculation in patients with lifelong PE.

CONCLUSION

In this study, we preliminarily identified the relevant sites by analyzing changes in the ALFF in patients with lifelong PE. Although our findings showed some interesting phenomena, more cases and more data are required to confirm whether fMRI is an objective indicator for identifying dapoxetine-sensitive patients with lifelong PE. However, the process of fMRI examination and data analysis was intricate, and the study was time-consuming and costly. It is no doubt that the further research needs to be optimized in the future. Analyzing ALFF changes in the brain by resting-state fMRI is an effective method to study PE. Even though our results showed ALFF changes in the brain areas of patients with lifelong PE could recover after administration of dapoxetine, it is still unclear whether there will be new findings by using other methods of data analysis. We hope this study provides some new ideas for studying PE and provides a reference for disease diagnosis and future research.

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STATEMENT OF AUTHORSHIP

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