



Higher inter-hemispheric homotopic connectivity in lifelong premature ejaculation patients: a pilot resting-state fMRI study

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Background: Lifelong premature ejaculation (PE) is one common male sexual dysfunction and is implicated in widespread structural and functional abnormalities of bilateral hemispheres. However, whether the inter-hemisphere functional connectivity (FC) of lifelong PE patients was altered still remain unclear.

Methods: Thirty-four lifelong PE patients and 30 healthy controls (HCs) were enrolled in this study and all underwent T1-weighted and resting-state functional MRI (fMRI) scan. The voxel-mirrored homotopic connectivity (VMHC) measure and independent sample *t*-test were applied to examine the alterations of VMHC values in the patients relative to HCs with the significant threshold at $P < 0.05$, false discovery rates corrected. Correlation analysis was adopted to calculate the relationships between the imaging results and clinical characteristics of patients ($P < 0.05$, Bonferroni corrected). Receiver operating characteristic (ROC) curve analysis was performed to investigate the possible biomarkers for distinguishing the patients from the HCs using the VMHC values of inter-group differences.

Results: The results revealed that compared with HCs, lifelong PE patients had higher VMHC values in the precentral gyrus (PG), primary somatosensory cortex (S1), supplementary motor area (SMA), precuneus, middle temporal cortex (MTC), superior temporal pole (STP), thalamus, caudate and middle cingulate cortex (MCC). Correlation analysis showed that the mean VMHC values in the S1 negatively correlated with intravaginal ejaculation latency time (IELT) in the patient group. Furthermore, the caudate revealed the well classification power from the ROC analysis.

Conclusions: The present study showed the abnormal inter-hemisphere interaction and integration of information involved in ejaculation inhibitory control, sensorimotor mediation and self-reference processing including the thalamus, caudate, MCC, widespread parietal cortex and temporal cortex in lifelong PE patients compared with HCs. Correlation analysis and ROC analysis revealed the importance of S1 and caudate in lifelong PE. Notably, the ROC result of caudate might show the core roles of caudate played in the pathophysiology of lifelong PE.

Keywords: Lifelong premature ejaculation (lifelong PE); resting-state functional MRI (resting-state fMRI); functional connectivity (FC); voxel-mirrored homotopic connectivity (VMHC)

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Introduction

Lifelong premature ejaculation (PE) is one common male ejaculation dysfunction disease, which affected 3% Chinese general male population (1) and seriously affected the life happiness of PE patients (2). It is defined as the ejaculation that always or nearly always happens within 1 minute of vaginal penetration as well as the insufficient ejaculation control (3). Substantial studies have reported the associations between the ejaculation and central nervous system (CNS) (4,5), indicating the important roles that neural mechanisms underlying lifelong PE such as abnormal central serotonergic neurotransmission plays in its pathology and related treatment (6). Meanwhile, studies have shown the effects of genetic (7), prenatal androgen (8) and psychology (9) on the occurring of lifelong PE. However, the exact pathophysiological mechanisms are still ambiguous.

Recently, the neuroimaging studies has investigated the structural and functional alterations in lifelong PE (or PE) patients, including (I) the anatomical abnormalities in the superior frontal gyrus, precentral gyrus (PG) and limbic system (the left anterior cingulate cortex and bilateral posterior cingulate cortex) (10) as well as caudate nucleus (11); (II) anomalous resting-state brain activity in the inferior frontal gyrus (IFG) and functional activation in the middle temporal cortex (MTC) associated with sexual response (12); aberrant brain current activity in the parahippocampal gyrus (13) and inferior occipital gyrus (14) related to erotic stimuli and sertraline treatment; (III) abnormal functional connectivity (FC) involved in the IFG (15), the MTC (12) and medial orbital frontal cortex (16), supplementary motor area (SMA) (17), insula (12,17), anterior and middle cingulate cortex (MCC), hypothalamus (18), caudate and putamen (19); (IV) and altered network characteristics, such as increased node degree in the right IFG and right MCC (17) as well as degree centrality (DC) in the insula and orbitofrontal cortex (20). Therefore, the aforementioned studies may suggest the central neural abnormalities, which may be implicated in the physiopathology of lifelong PE. However, the neuroimaging studies on the CNS of lifelong PE patients remain incomplete.

Voxel-mirrored homotopic connectivity (VMHC) (21) is a new measure based on resting-state functional MRI (fMRI) and is proposed to examine the degree of functional homotopy (22,23) between the brain regions of geometric correspondence located on the bilateral hemispheres. Meanwhile, the functional homotopy has been suggested to be a critical characteristic of brain intrinsic connectivity

architecture (23) and VMHC is devised to test the aberrant pattern of inter-hemisphere intrinsic connectivity by calculating the correlations between the resting-state fMRI recorded blood oxygen level dependent signals (21,24) of homotopic regions. The differences of VMHC values between different bilateral homotopic regions are considered to reveal the different characteristics of inter-hemisphere information interaction involved in sensation and motor coordination (23). VMHC has been regarded as a reliable approaches and has been applied to several diseases to characterize the abnormal homotopic intrinsic FC that could underly the pathological mechanisms, such as autism (25), Parkinson's disease (26) and traumatic axonal injury (27). The corpus callosum is the largest fiber tract connecting the two cerebral hemispheres and coordinates the information from the both hemispheres (28). The latest structural imaging research of lifelong PE has reported outward shape expansions in the bilateral thalamus (29), which is supposed to play important roles in the etiology of lifelong PE (30) and has cortex connectivity with the corpus callosum (31). Meanwhile, the lifelong PE patients have revealed multiply structural and functional abnormalities in the widespread bilateral brain regions (10,16,17,20). These raised a question: whether the whole-brain inter-hemisphere intrinsic FC of lifelong PE patients is altered?

Therefore, the aims of this study were to investigate the differences of functional coordination between the two hemispheres in lifelong PE patients and to examine whether there were significant correlations between imaging results and clinical characteristics. In this study, we hypothesized that the inter-hemisphere FC revealed by aforementioned VMHC values would be altered in lifelong PE patients compared with healthy controls (HCs) and the resultant VMHC values would correlate clinically.

Methods

Participants

Thirty-four lifelong PE patients and 30 HCs were included in this study. Physical examination was applied to every participant and all participants did not receive any treatment of PE. The exclusion criteria for all participants comprised: (I) having neurological or psychiatric disease; (II) having a history of alcohol, nicotine or medicine abuse; (III) having trauma; and (IV) having any contraindication of MRI scanning. The inclusion criteria for patients comprised: (I) heterosexual males (32); (II) the average of intravaginal

ejaculation latency time (IELT) over past 2 weeks <1 minute, measured by female sexual partner using stopwatch; (III) Premature Ejaculation Diagnostic Tool (PEDT) score >11 (33,34); (IV) International Index of Erectile Function-5 (IIEF-5) score >21 (35). The inclusion criteria for HCs comprised: (I) heterosexual males (32); (II) PEDT score <5; (III) IIEF-5 score > 21; (IV) age- and hand dominate-matched with patient group. Furthermore, Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) were adopted to investigate their anxiety and depression level (36,37).

Image data acquisition

All participants' imaging data were acquired based on a 3.0T GE MRI system (EXCITE, Milwaukee, WC, USA) at the local hospital. A standard 8 channel birdcage head coil was adopted and foam pads were used to restrain head motion. The high resolution T1 image data were acquired using the 3D spoiled gradient echo with the parameters set as follows: field of view (FOV) =256×256 mm²; slice thickness 1 mm; data matrix =256×256; repetition time (TR) =8.2 ms, echo time (TE) =3.2 ms; flip angle (FA) =12°; in-plane resolution =1×1 mm². The resting-state fMRI image data were acquired using the single-shot gradient echo with the parameters set as follows: FOV =240×240 mm²; slice thickness 3.5 mm with no gaps; matrix size =64×64; TR =2,000 ms, TE =30 ms; FA =90°; in-plane resolution =3.75×3.75 mm²; 45 axial slices. During scanning, each participant was required to keep in the supine position and think about nothing during the resting imaging.

MRI data preprocessing

The preprocessing of fMRI data were performed using DPABI (V4.1, <http://rfmri.org/dpabi>) (38) and Statistical Parametric Mapping 12 (spm12, <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) software package based on the platform of MATLAB. Briefly, the following steps were conducted: (I) removal of first 5 time points; (II) correction of slice timing; (III) correction of head motion using rigid body transformation; (IV) spatial normalization to the MNI space using the standard echo planar imaging template and resampling the images at 3×3×3 mm³ voxel size (39); (V) smoothing with a Gaussian kernel (6 mm full-width at half maximum); (VI) removal of linear detrending and bandpass filtering (0.01–0.1Hz); (VII) nuisance covariates regression including 24 head motion parameters and the signals of white

matter, cerebrospinal fluid signals and global brain. After motion correction, all participants enrolled in the following data processing had shorter than 2 mm translation in the X, Y or Z-axis or 2° of angular rotation. Furthermore, the framewise displacement (FD) (40) of the two groups were examined and showed no inter-group differences in mean head motion.

VMHC analysis

VMHC measure supposed that the bilateral hemispheres had symmetrical morphology. The normalized T1 images of all participants were averaged and the resultant mean T1 image was further averaged with its left-right mirrored version to create the group-specific identical structural template. The above preprocessed functional images were then transformed to register to the new identical template. The VMHC calculation was conducted with software DPABI (38). The VMHC was computed as the Pearson correlations between pairs of symmetrical voxels of the two hemispheres, after which Fisher *r*-to-*z* transformation was adopted to improve the normality of the correlation coefficients and to generate the final VMHC map for each participant.

Statistical analysis

Statistical Product and Service Solutions (SPSS) version 20.0 (IBM Corporation, Armonk, New York, NY, USA) was applied to examine the inter-group differences of the key clinical characteristics (age, IELT, PEDT score, IIEF-5 score, SAS and SDS) using two-tailed two sample *t*-test. The significant level was set as *P*<0.05.

To test the differences of VMHC between the two groups, one sample and two sample *t*-test were used to restrict the imaging results to the brain regions with positive VMHC (41) and the inter-group contrasts adopted the threshold as *P*<0.05 (FDR corrected with the age, anxiety, depression factors as covariates). The brain regions showing significant differences from above *t*-tests were supposed as regions of interest (ROIs). Correlation analysis with and without emotional factors (e.g., SAS and SDS) as covariates was used to test the association between the mean VMHC values of the ROIs and clinical characteristics, such as PEDT scores and IELT (*P*<0.05, Bonferroni corrected). Furthermore, receiver operating characteristic (ROC) curves analysis (42) was performed using the mean VMHC values from the ROIs to figure out the possible biomarkers for separating the patients from HCs, including

the characteristics of sensitivity, specificity and area under the curve (AUC) (43). Nonparametric permutation test was used to examine the statistical significance and $P < 0.05$ was considered to be significant in the ROC analysis.

Results

Clinical characteristics results

The statistical results of demographic and clinical characteristics of all the participants were shown in *Table 1*.

Table 1 Demographic and clinical characteristics of all participants

Characteristics	PE (n=34)	HCS (n=30)	P value
Ages (years)	31.18±5.21	31.70±2.91	0.628
IELT (min)	0.64±0.23	11.00±5.55	0.000***
PEDT score	17.06±1.71	0.73±1.44	0.000***
IIEF-5 score	23.97±0.87	24.27±1.34	0.292
SAS	38.88±4.06	30.47±1.68	0.000***
SDS	40.97±3.44	30.50±2.13	0.000***

Data were expressed as the mean ± SD. ***, $P < 0.001$ by independent sample *t*-test. PE, premature ejaculation; HCs, healthy controls; IELT, intravaginal ejaculatory latency time; PEDT, Premature Ejaculation Diagnostic Tool; IIEF, International Index of Erectile Function; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; SD, standard deviation.

No significant inter-group differences were observed in age and IIEF-5 scores (all $P > 0.05$). The IELT, SAS and SDS scores significantly differed between the two groups (all $P < 0.001$).

Inter-group VMHC comparison

Compared with HCs, lifelong PE patients showed significantly higher VMHC values in the PG, primary somatosensory cortex (S1), SMA, precuneus, MTC, superior temporal pole (STP), thalamus, caudate and MCC (*Figure 1* and *Table 2*).

Correlation analysis

Based on the inter-group VMHC results, correlation analysis showed that the mean VMHC values in the S1 negatively correlated with IELT ($r = -0.38$, $P = 0.026$, uncorrected) (*Figure 2A*) in the patient group. After accounting for the emotional factors, the aforementioned significant correlation was still observed ($r = -0.47$, $P = 0.005$, Bonferroni corrected) (*Figure 2B*). Furthermore, the ROC analysis revealed the AUC in caudate was 81.7% with a specificity of 87.2% and a sensitivity of 65.3% (*Figure 3*).

Discussion

Compared with HCs, we investigated the altered VMHC

Table 2 Brain regions with higher differences in VMHC in lifelong PE patients compared with HCs

Brain regions	MNI			BA	Cluster size	T value
	X	Y	Z			
Precuneus	15/-15	-42	72	1,5	221	4.37
S1	18/-18	-39	75	1,2,3	677	4.19
Thalamus	15/-15	-15	12	-	223	4.09
SMA	9/-9	-9	72	6	224	3.69
STP	48/-48	15	-21	38	105	3.57
PG	24/-24	-9	66	6	273	3.54
MTC	54/-54	-24	-3	21	436	3.50
Caudate	15/-15	9	21	-	153	3.48
MCC	3/-3	-24	39	23	192	3.42

VMHC, voxel-mirrored homotopic connectivity; PE, premature ejaculation; HCs, healthy controls; MNI, Montreal Neurological Institute; BA, Brodmann area; (X, Y, Z), coordinate of peak location in the MNI space; T, statistical value of peak voxel; S1, primary somatosensory cortex; SMA, supplementary motor area; STP, superior temporal pole; PG, precentral gyrus; MTC, middle temporal cortex; MCC, middle cingulate cortex.

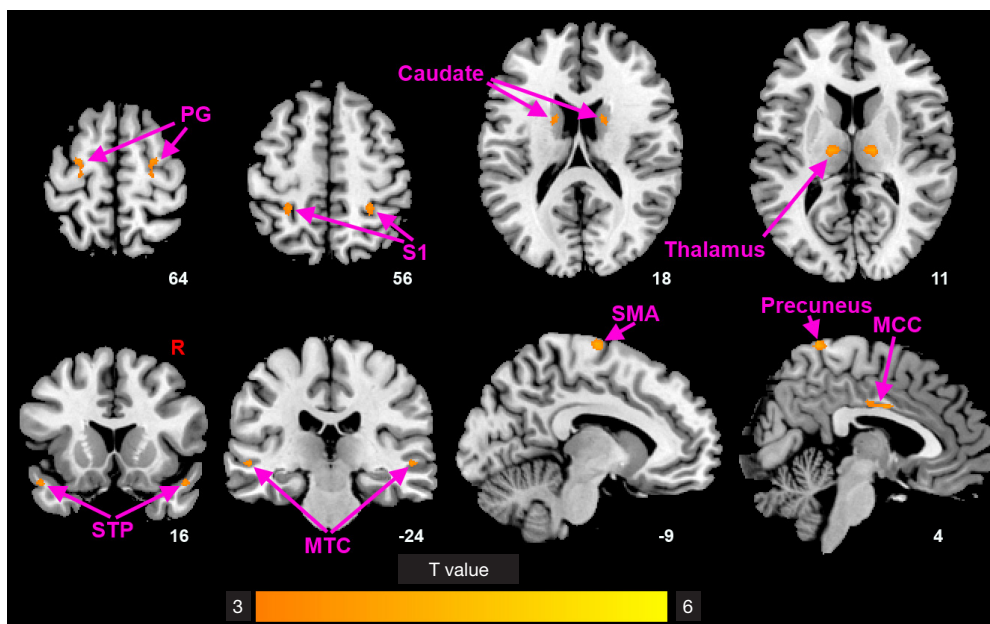


Figure 1 Brain regions showing significantly altered VMHC values in the lifelong PE patients compared with HCs. VMHC, voxel-mirrored homotopic connectivity; PE, premature ejaculation; HCs, healthy controls; PG, precentral gyrus; S1, primary somatosensory cortex; STP, superior temporal pole; MTC, middle temporal cortex; SMA, supplementary motor area; MCC, middle cingulate cortex; R, right.

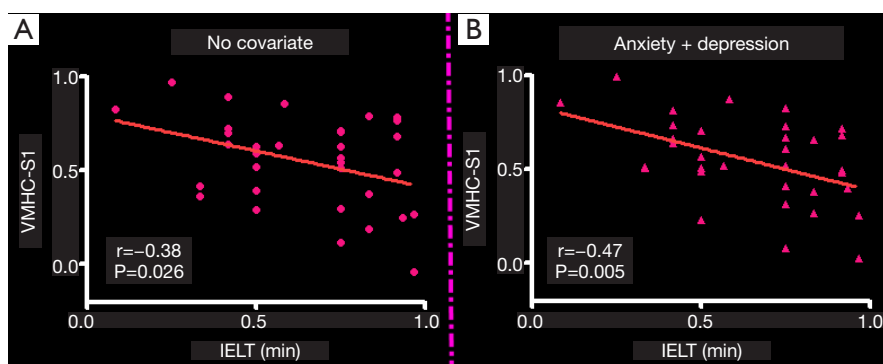


Figure 2 Correlations results. (A) Positive correlation between the VMHC values in the S1 and IELT in the patient group (with no covariate). (B) Positive correlation between the VMHC values in the S1 and IELT in the patient group (with the anxiety and depression scores as covariates). VMHC, voxel-mirrored homotopic connectivity; S1, primary somatosensory cortex; IELT, intravaginal ejaculatory latency time.

of lifelong PE patients using the VMHC measure and the inter-group statistical analysis results showed that the higher VMHC values were found in the PG, S1, SMA, precuneus, MTC, STP, thalamus, caudate and MCC than in the HCs. The mean VMHC values of S1 had significant correlation with IELT and the VMHC values of caudate revealed well power to differentiate lifelong PE patients from the HCs.

In this study, the higher VMHC values in temporal regions

including the MTC and the STP were found in lifelong PE patients than in the HCs. Male sexual behavior is reported as a complex process involved in the excitation, erection and the ejaculation stage. Ejaculation is the culmination of sexual behavior and mediated by special regions implicated in sensory or sexual inhibition (15). Healthy males showed increased brain activity of temporal cortex after ejaculation (44). The temporal cortex is associated with visual information and

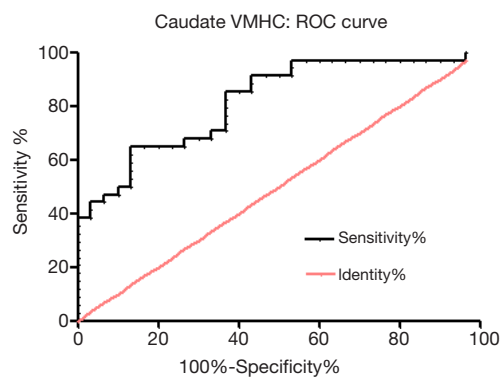


Figure 3 ROC curve analysis of the mean VMHC values of caudate. The AUC for caudate was 81.7% with a specificity of 87.2% and a sensitivity of 65.3%. ROC, receiver operating characteristic; VMHC, voxel-mirrored homotopic connectivity; AUC, area under the curve.

autonomic processing (45). Numerous studies have revealed the dysfunction of temporal cortex in PE patients (12,16-19). For example, a recent PE study has reported the increased activation in right MTC during sexual picture stimuli compared with scenery picture stimuli (12). Meanwhile, decreased current source density (CSD) in the left MTC (13) was found in another PE studies during sexual video stimuli using HCs as baseline. Therefore, the temporal cortex dysfunction might be important in lifelong PE and be mainly involved in the abnormalities of ejaculation inhibitory control. Furthermore, the recent lifelong PE study showed the increased right MTC-seeded FC in the multiple regions including the left MTC compared with HCs (46), which was consistent with our imaging results found here.

We observed that lifelong PE patients had higher VMHC values in the S1, thalamus, SMA, PG and MCC in this study. Ejaculation is a motivated process and the alteration of penis sensitivity is an important feature of PE. The abnormalities of genital somatosensory information processing are highly involved in sexual dysfunction (47). Thalamus is the crucial region associated with homeostatic, motivational and visceral sensory response (48), which is also involved in the androgen receptor expression and participants in the spinal cord control of ejaculation (49). Neuroimaging study has revealed that the sensory information output from the penis is transmitted to the spinal ejaculation center, the thalamus and finally to the S1 (50). Healthy males showed increased activation in somatosensory cortices by viewing sexual scenes (51).

Lifelong PE patients had decreased FC density in thalamus (17) as well as decreased FC involved in S1 (16). Furthermore, genital stimuli induced increased brain activation in sensory and motor cortex including the S1 and premotor cortex in HCs (52). Meanwhile, a recent study reported the increased excitability of motor cortex whether in heterosexual or homosexual healthy males (53) by visual sexual stimuli, which revealed the participation of motor except aforementioned sensory in sexual behavior. The SMA and PG are typical motor association cortex. Lifelong PE patients showed abnormal increased thickness in bilateral PG (10) and increased long-range FC density in bilateral SMA as well (12) as increased right MTC-seed FC in bilateral SMA in lifelong PE patients compared with HCs (17). The cingulate cortex participants in sexual erection process (54) and the MCC is involved in sensorimotor processing revealed by its strongly connectivity with regions related to sensory and motor, such as insula and SMA (55). The functional abnormalities of bilateral MCC have been found in lifelong PE patients (12,17). Therefore, studies mentioned above may indicate the important roles that S1 and thalamus play in sensory processing as well as SMA and PG play in motor preparation processing of lifelong PE pathology besides the MCC in sensorimotor. The greater VMHC values found in S1, thalamus, SMA, PG and MCC might represent the abnormal inter-hemisphere functional interaction and integration associated with sensorimotor processing and might compensate for other brain functions. Furthermore, the mean VMHC values extracted from the S1 were negatively correlated with the IELT in the patient group with and without accounting for emotional factors, which might highlight the special roles of S1 plays in the pathology of lifelong PE.

In this study, lifelong PE patients showed higher VMHC in the precuneus, caudate compared with HCs. Parietal cortex is mainly involved in somatosensory and visual-spatial processing (56). Specially, precuneus is located in the posteromedial parietal cortex and is associated with the visual-spatial perception as well as self-consciousness and self-related mental processing (57). Healthy males had increased regional cerebral brain flow (rCBF) in the right precuneus during ejaculation relative to sexual stimuli (5). Lifelong PE patients showed increased DC in the bilateral precuneus compared with HCs (20). Caudate is the important part of striatum and play roles in sex-related reward and motor-mediation processing (58). Structural study of lifelong PE patients found larger mean volume

in caudate (11) in the patient group compared with HCs. Meanwhile, lifelong PE patients had decreased FC between the right caudate and multiple regions involved in abnormal sensory and reward processing using HCs as baseline (19). In addition, lifelong PE patients revealed increased long-range FC density in the bilateral precuneus compared with HCs as well as decreased short-range FC density in the left caudate (17). Therefore, the higher VMHC values found in precuneus and caudate might indicate the inter-hemisphere functional abnormalities involved in the self-reference information processing of sexual stimuli of lifelong PE. Furthermore, the ROC analysis showed that the caudate of the lifelong PE patients and HCs had the quite well performance to distinguish the patients from HCs with the AUC of 81.7%, indicating the VMHC values from the caudate could be potential biomarkers for lifelong PE and suggesting the core participation of caudate dysfunction in the pathophysiological process of lifelong PE.

Limitations

There are several limitations in this study. First, the results of the current findings were generated from a relatively small sample data of the patients and HCs. Second, whether the VMHC abnormality found in this study was the cause or the outcome of lifelong PE was still unclear. Third, this study is a cross sectional study, the dynamic process of VMHC alterations was unable to be observed. Furthermore, this study was not applied principal component and much descriptive statistics analyses, which might improve the validation of the original presumptions (59). Thereby, further studies with larger number of participants and longitudinal data are needed to validate and perfect our findings as well as the application of analyses related to component and multivariate statistics.

Conclusions

Our present study provided evidences that patients with lifelong PE had the abnormal inter-hemisphere interaction and integration of information involved in ejaculation inhibitory control, sensorimotor mediation and self-reference processing in widespread cortex (e.g., MTC, STP, S1, SMA and PG) and subcortex regions (e.g., thalamus, caudate and MCC) compared with HCs. The statistical results of the correlation and ROC analysis using imaging findings might indicate the importance of S1 and caudate in lifelong PE. Especially the result from the ROC analysis

might explore the core roles of caudate played in the pathophysiology of lifelong PE.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/qims-20-1103>). The authors have no conflicts of interest to declare.

Ethical Statement: The ethical committee of the Northwest Women's and Children's Hospital in China approved the all procedures of this study (No. 2017014), and which was in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants provided the written informed consents before the experiment began.

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