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Abnormal White Matter Microstructure in Lifelong Premature Ejaculation Patients Identified by Tract–Based Spatial Statistical Analysis

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ABSTRACT

Introduction: Several recent neuroimaging studies have identified functional and structural abnormalities in the cerebral cortex of lifelong premature ejaculation (LPE) patients, including task-related and resting-state brain function, and cortical thickness, although changes in white matter microstructure have not been reported.

Aim: To assess the differences in white matter microstructure between LPE patients and healthy controls.

Methods: Diffusion tensor imaging (DTI) and tract-based spatial statistical analysis were used to detect differences in white matter microstructure between 32 LPE patients and 32 matched healthy controls. We also analyzed correlations of clinical indices with significant DTI–based features.

Main Outcome Measures: DTI–based features (including fractional anisotropy [FA], mean diffusivity, axial diffusivity, and radial diffusivity) were assessed in LPE patients and controls, as well as the correlation of white matter changes in LPE patients with clinical data (including the premature ejaculation diagnostic tool score and the International Index of Erectile Function).

Results: LPE patients showed widespread increases in FA and axial diffusivity values compared with controls, including in the right posterior thalamic radiation, posterior corona radiata, bilateral posterior limb of the internal capsule, superior corona radiata, and external capsule. Further, FA in the right posterior thalamic radiation was positively correlated with the premature ejaculation diagnostic tool score in LPE patients.

Clinical Implications: Changes of white matter microstructure may be an underlying marker for evaluating sensory conduction efficiency in LPE patients.

Strengths & Limitations: There are no previous studies examining white matter microstructure in LPE patients. The present study furthers our understanding of the etiology of LPE. Limitations include a cross-sectional study design without causal information, and no measurement of conduction efficiencies such as cortical somatosensory-evoked potential from the penis, or psychosocial factors.

Conclusion: Our findings show potential microstructural white matter abnormalities related to LPE, suggesting that changes in fiber pathways connecting the cerebral cortex and the thalamus may play roles in the etiology of LPE. **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;15:1272–1279.**

Key Words: Lifelong Premature Ejaculation; White Matter; Diffusion Tensor Imaging; Premature Ejaculation Diagnostic Tool

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INTRODUCTION

Lifelong premature ejaculation (LPE) is a common male sexual dysfunction, characterized by ejaculation that always or nearly always occurs prior to or within approximately 1 minute of vaginal penetration since the first sexual experience.[1,2] The prevalence of LPE is 5% globally, and 3% in China.[3] To date, the biological mechanism of this disorder remains unclear. The etiology of premature ejaculation (PE) was original considered to be related to hyperesthesia of the glans penis, abnormal local anatomy of the urogenital apparatus, or psychosomatic disturbance.[4] However, in recent years, there is increasing evidence for genetic and neurological mechanisms. For example, several candidate single nucleotide polymorphisms in the serotonin transporter gene, the serotonin 1A or 2C receptor genes, and the dopamine transporter gene may contribute to the intravaginal ejaculation latency time of LPE, although these findings remain controversial.[5–8] In addition, the widespread use of serotoninergic and dopaminergic drugs for clinical treatment of PE has prompted investigation of the potential central nervous system abnormalities in PE patients. However, the majority of these hypotheses are speculative and based on the central mechanism of ejaculation.[7,9–11] Direct evidence from PE remains insufficient, although a recent electrophysiology study reported abnormal vision-evoked brain electrical activity in PE patients.[12]

There is now increasing use of neuroimaging techniques, including positron emission tomography and magnetic resonance imaging (MRI), in studying the neuroanatomical basis of human sexual behavior in normal subjects and patients with sexual dysfunction. In healthy subjects, consistent neural activation has been observed in a wide range of cortical and subcortical areas in response to sexual arousal, including the occipitotemporal, inferotemporal, parietal, prefrontal, and insular cortices, and areas in the cerebellum and limbic system.[13] Normal ejaculation behavior has also been related to de-activation throughout the prefrontal cortex.[14,15] By contrast, abnormal activation of cortical and subcortical brain function during erotic stimulation was reported in psychogenic erectile dysfunction (pED) (patients with persistent inability to achieve or maintain an erection satisfactorily for sexual performance, predominantly or exclusively because of psychological or interpersonal factors),[16,17] while a distinct pattern of brain activation was also observed in LPE patients compared with healthy controls in a vision task[18] and an inhibitory control task[19] functional MRI studies.

A number of other studies have directly evaluated the brain structure and spontaneous brain function of pED and LPE patients, in which pED patients presented an abnormal map of gray matter and white matter and baseline brain activity (assessed by the amplitude of low-frequency fluctuations),[20–24] and LPE patients showed decreased cortical thickness and aberrant spontaneous brain activity (assessed by regional homogeneity and functional connectivity).[18,25,26] These preliminary findings suggest a role for abnormal brain structure and function in the neurobiological mechanisms of LPE. Considering the key role of white matter regions of the brain in neural information communication, there is also potential for microstructural changes in the white matter in LPE patients, although this is currently unknown.

In the present study, we investigated the differences in white matter microstructure between LPE patients and matched healthy controls using diffusion tensor imaging (DTI) and tract-based spatial statistics (TBSS). DTI—based features such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) are useful for characterizing white matter microstructure.[27–29] We also performed a correlation of white matter changes in LPE patients with clinical data.

METHODS

Subjects

A total of 64 right-handed adult men including 32 untreated LPE patients and 32 healthy controls were recruited. LPE was diagnosed according to the International Society for Sexual Medicine guidelines for the diagnosis and treatment of PE[2] and the PE diagnostic tool (PEDT). PEDT is a brief, multidimensional, psychometrically validated instrument for the diagnosis of PE, and consists of 5 items. Sensitivity and specificity analyses suggest a score $\leq$8 indicates no PE, 9 and 10 indicates probable PE, and $\geq$11 indicates PE.[30] In the present study the PEDT score was >11 in LPE patients and <9 in controls. The intravaginal ejaculation latency time (IELT) was determined by stopwatch,[31] and was <1 minute for each LPE patient. All participants underwent history taking and physical examination to exclude a history of neurological or other psychiatric disorders, head trauma, or mental diseases. All participants had a normal International Index of Erectile Function score.[32] Participants were excluded if they were dependent on any drugs or alcohol, had a medication history of selective serotonin reuptake inhibitors, or any contraindication to MRI scanning. All participants provided written informed consent. Research procedures were approved by the ethical committee of the Northwest Women's and Children's Hospital in China, and were conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

MRI Acquisition

Individual DTI data were acquired on a 3-T full-body scanner (EXCITE, General Electric, Milwaukee, WI, USA) located at Xijing Hospital (Xi'an, China), and equipped with an 8-channel receiver head coil. DTI data were scanned using the following parameters: repetition time/echo time = 10,000/85.3 milliseconds, field of view = 240 × 240mm^2, matrix size = 256 × 256, slice thickness = 2 mm, and 70 continuous axial slices with no gap. 2 Diffusion-weighted sequences were acquired using