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Short- and long-range synergism disorders in lifelong premature ejaculation evaluated using the functional connectivity density and network property

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ABSTRACT

This study was aimed to investigate brain function connectivity in premature ejaculation (PE) patients using the functional connectivity density (FCD) and network property of resting-state functional magnetic resonance imaging. Twenty PE patients (mean age: 27.95 ± 4.52 years) and 15 normal controls (mean age: 27.87 ± 3.78 years) with no self-reported history of neurologic or psychiatric disease were enrolled in this study. International Index of Erectile Function-5 and Chinese Index of Sexual Function for Premature Ejaculation-5 questionnaires and self-reported intravaginal ejaculatory latency time (IELT) were obtained from each participant for symptom assessment. Two-sample *t*-tests (intergroup comparison) were applied in the short-range FCD (SFCD) analysis, long-range FCD (LFCD) analysis, region of interest–based analysis, and network topological organization analysis. Pearson correlation analysis was performed to correlate IELT with FCD or the network property. The patients with PE showed significantly decreased SFCD in the bilateral middle temporal gyrus, left orbitofrontal cortex, nucleus accumbens, fusiform, caudate, and thalamus ($p < 0.05$, AlphaSim-corrected). Notably, all these aforementioned brain areas are located in the dopamine pathway. In contrast, increased LFCD was observed in the left insula, Heschl's gyrus, putamen, bilateral precuneus, supplementary motor area, middle cingulate cortex, and anterior cingulate cortex in PE patients ($p < 0.05$, AlphaSim-corrected). In addition, the network topological analysis found reinforced network connectivity between several nodes. The degree of hub nodes increased in the patients with PE. IELT was positively correlated with SFCD and negatively correlated with LFCD or the degree of hub nodes ($p < 0.05$, Pearson correlation). In summary, our results are important for understanding the brain network in PE patients. The present findings indicate that PE patients have a significant synergism disorder across the region of dopamine pathway, which implied neuronal pathological changes might be related with the change of dopamine. The FCD and network property can serve as new disease severity biomarkers and therapeutic targets in PE.

1. Introduction

Ejaculatory dysfunction, particularly premature ejaculation (PE), is considered the most common type of male sexual disorder (Laumann et al., 2005; Saitz and Serefoglu, 2015), and affects 20–30% of men of all ages (Gur and Sikka, 2015). Using an evidence-based unified definition, the International Society for Sexual Medicine defines PE as a male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within 1 min of vaginal penetration from the first sexual experience (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to approximately 3 min or less (acquired PE) (Serefoglu et al., 2014). However, the understanding of the epidemiology, pathophysiology, and management of this disorder remains limited (Serefoglu and Saitz, 2012).

Although the noninvasive and objective functional brain imaging techniques, like functional magnetic resonance imaging (fMRI) have largely developed in recent decades, there is scarce data on brain functional changes in patients with PE. In recent years, increasing attention has been focused on using task or resting-state functional magnetic resonance imaging (rs-fMRI) to detect brain response and

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activity in patients. Interestingly, several studies have used task-based fMRI to examine the brain response to visual sexual stimuli in healthy men and found an increased response in the parietal lobes, temporal lobes, parieto-occipital sulcus, superior occipital gyrus, anterior cingulate gyrus, insula, amygdala, and septal areas (Kim et al., 2006; Mallick et al., 2007; Mouras et al., 2003). These studies indicate that at a macro level, various brain areas are involved in the ejaculatory behavior process (Coolen et al., 1997). In addition, other studies with task-based fMRI demonstrate that the ejaculatory behavior process employs a complex interconnected network comprising the hypothalamic, diencephalic, and pontine areas (Gur and Sikka, 2015). However, how these brain areas interact during the ejaculatory behavior process and whether these brain areas are coordinated with some particular brain systems remain unclear.

The complex task paradigm is required in the aforementioned studies with task-based fMRI. However, based on functional connectivity density (FCD) mappings, rs-fMRI can detect intrinsic activity in the brain with simple cooperation of the subjects. In fact, data-driven FCD is ideal for exploratory analysis because it quantifies the strength of the local functional connectivity hubs (network nodes with high connectivity to nearby brain regions) and does not rely on priory hypothesis (Biswal et al., 1995; Tomasi and Volkow, 2010). Moreover, the graph theoretical analysis can provide a unique framework for measuring brain networks and has therefore gained popularity in neuroimaging and brain network studies. Notably, the graph theoretical analysis in highly connected hub regions of functional networks (Tomasi and Volkow, 2010, 2012) can overcome the limitations of seed-based approaches for the identification of hubs in the human brain. Therefore, it would be valuable to investigate the activity disorder at a connected hub and network level.

Our previous study with combined rs-fMRI and task-based fMRI analysis has found aberrant brain responses and impaired functional integration in certain brain areas in PE patients (B. Zhang et al., 2017). However, it remains unclear whether the brain areas identified in the previous study can be integrated into some specific neuro systems. In this study, we used the rs-fMRI data from the previous datasets to explore pathophysiological mechanisms in PE by FCD and network-based graph theoretical analysis. We hypothesized that 1) patients with PE had different patterns of FCD mapping compared with normal controls (NCs). 2) In addition, the topological organization of brain network, such as network global or local efficiency, small-world property, or nodal degree, will be changed in functional connectivity networks composed of hubs in PE patients.

2. Materials and methods

2.1. Participants

From 2012 to 2014 in the Nanjing Drum Tower Hospital, 20 right hand-dominant patients with lifelong PE and 15 right hand-dominant healthy controls were enrolled in this study. The detailed information about these participants can be found in our previous work (B. Zhang et al., 2017). Briefly, the lifelong PE patients were diagnosed according to ISSM guidelines (Serefoglu et al., 2014): a) ejaculation that always or nearly always occurs prior to or within about 1 min of vaginal penetration; b) the inability to delay ejaculation on all or nearly all vaginal penetrations; and c) negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy. Fifteen healthy subjects were enrolled in this study as controls, with self-reported intravaginal ejaculatory latency time (IELT) of > 3 min. The IELT was measured for the 4-week baseline period during which both patients and NCs were asked to have sexual intercourse at least 4 times. Patients with erectile dysfunction (International Index of Erectile Function [IIEF]-5 score < 21), reduced sexual desire, or inhibited male orgasm were excluded from the study. Moreover, patients with mental disorders, physical illnesses which affect ejaculatory function, abuse of alcohol, and any medical treatment for premature ejaculation in the past 6 months were excluded. All the subjects completed the following two questionnaires: IIEF-5 (Rhoden et al., 2002) and Chinese Index of Sexual Function for Premature Ejaculation (CIPE)-5 questionnaires (Yuan et al., 2004). This study was conducted according to the Declaration of Helsinki and approved by the institutional review boards of the Nanjing Drum Tower Hospital. Written informed consent was obtained from each subject.

2.2. Image acquisition

The fMRI experiment was performed with an Achieva 3.0 T (TX) MR system, and the acquisition parameters of resting state fMRI were set as follows: field of view (FOV) = $192 \times 192\,mm^2$; section thickness = 4 mm with no section gap; matrix = 64×64; repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; and flip angle = 90°. A total of 230 volumes were acquired, and each volume included 35 transverse slices covering the whole brain. During the resting state fMRI scanning, each subject was requested to lie quietly with his eyes closed. In addition, the high-resolution 3D T1-weighted brain structural images were also acquired for each participant, and the acquisition parameters were set as follows: TR = 7600 ms; TE = 3400 ms; flip angle = 8°; FOV = $256 \times 256 \times 192\,mm^3$; and slice thickness = 1 mm.

2.3. Image preprocessing

The fMRI data were processed with Data Processing Assistant for Resting-State fMRI, advanced edition [http://rfmri.org/DPARSFA] (Yan and Zang, 2010), which is based on Statistical Parametric Mapping (http://www.fil.ion.ucl.ac.uk/spm) and the toolbox for Data Processing & Analysis of Brain Imaging [DPABI, http://rfmri.org/DPABI] (Yan et al., 2016). Slice timing, head motion correction, and spatial normalization to the standard Montreal Neurological Institute (MNI) EPI template with a resolution of $3 \times 3 \times 3\,mm^3$ were conducted. According to the study by Anderson et al. and Murphy et al., the global signal regression was not performed to avoid introducing distortions into the time-series data (Anderson et al., 2011; Murphy et al., 2009). The included subjects had head movement < 3 mm translation or $< 3°$ angular rotation in any axis during fMRI scanning. Subsequently, the data were detrended to remove the linear trend of time courses and band-pass filtered (0.01–0.08 Hz).

2.4. FCD mapping

In the present study, the FCD definition was based on the previous study by Tomasi and Volkow (2010, 2012). Usually, the FCD is divided into short-range FCD (SFCD) and long-range FCD (LFCD). The SFCD reflects the FC between voxels within a local cluster (intraregional), while LFCD reflects the FC between a voxel within a local and the other without the local cluster (interregional) (Z. Zhang et al., 2017). The detailed computing procedure about SFCD and LFCD can be found in Tomasi's study (Tomasi and Volkow, 2011). In brief, to calculate the SFCD, we computed Pearson's correlations between the time course at x_0 and those at its local neighbors. A voxel (x_j) was added to the list of neighbors of x_0 only if it was directed linked to x_0 with the correlation factor $R_{0j} > 0.6$. This calculation was repeated for all voxels that were adjacent to voxels that belonged to the list of neighbors of x_0 in an iterative manner until no new neighbors could be added to the list. The