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Neuroimaging biomarkers of psychogenic erectile dysfunction: protocol for a systematic review
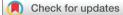
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ABSTRACT

Introduction Erectile dysfunction (ED) is the most common male sexual disorder that severely impacts the sexual performance and quality of life of men. As the main subtype of ED, psychogenic ED (pED) has been demonstrated to be a genitourinary disease and also associated with alterations in both brain structure and function. However, the scattered neuroimaging evidence from individual studies has not yet been integrated, and the central pathological alterations associated with pED remain unclear. The objective of this systematic review is to integrate and assess the evidence of the impact of pED on brain structure and function.

Methods and analysis Five databases (PubMed, EMBASE, Web of Science, China Biology Medicine Database and China National Knowledge Infrastructure (CNKI)) will be systematically searched from inception to 1 October 2019 (the anticipated completion date of this review), with language restricted to English and Chinese. Studies focusing on the structural or functional alterations in patients with pED will be retrieved. The study selection process will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline and quality assessment will be conducted with a customised checklist. After data extraction, a qualitative review will be performed to synthesise the structural and functional brain alterations as well as the correlations between the altered cerebral structures and functions and the clinical characteristics of patients with pED. If the collected data make it feasible, an activation likelihood estimation meta-analysis will also be launched.

Ethics and dissemination Ethical approval is not required as primary data will not be collected. This review will be published in a peer-reviewed journal and presented at conferences.

PROSPERO registration number CRD42019117206.

Strengths and limitations of this study

► This is the first systematic review and meta-analysis that integrates and assesses the central pathological characteristics of psychogenic erectile dysfunction.
► Qualitative and quantitative synthesis (activation likelihood estimation meta-analysis) will both be used in this study.
► A customised checklist is proposed to evaluate the quality of the included studies according to the purpose of this review.
► This review does not restrict the race, age, disease conditions of participants or preprocessing procedures of included studies, which will increase the heterogeneity of included studies and may increase the risk of bias of the review.

dysfunction.[4] As a physical and psychosocial illness, ED not only impairs male sexual confidence and satisfaction but also severely impacts the quality of life (QoL)[5 6] and relationships[7] of patients and their partners. More importantly, ED has been increasingly regarded as an independent risk factor for cardiovascular diseases.[8 9] According to its different causes,[10 11] ED is subdivided into psychogenic ED (pED), organic ED and mixed ED. Different from organic ED, which has clear causes and pathological characteristics, pED is generally caused by uncertain psychological factors[12 13] and lacks specific biomarkers.

Rationale for review

Penile erection is a complex physiological process modulated by the central nervous system and mediated by several neurotransmitters and neuropeptides.[14 15] A meta-analysis identified that penile erection was regulated by several cerebral regions; the activities of the insular cortex, claustrum, putamen and anterior midcingulate cortex were consistently positively correlated with male penile erection.[16] With the close relationship between the brain and penile erection being widely

INTRODUCTION

Erectile dysfunction (ED) is the most common male sexual disorder. It is characterised by the persistent inability to attain or maintain an adequate erection to obtain satisfactory sexual intercourse regardless of the capability of ejaculation.[1–3] According to epidemiological studies, approximately 37% of men over 70 years old and 11% of men over 30 years old suffer from this sexual

accepted, using neuroimaging techniques to explore the central pathological characteristics of pED has attracted the attention of many researchers.[17–22] In the process, some well-designed cognitive-behavioural models have been developed to further explain the neurobiological underpinning of abnormal behaviour in patients with ED.[23 24] For example, two task functional MRI (fMRI) studies focusing on male sexual arousal reported that, when compared with healthy controls, patients with pED manifested lower penile tumescence, more activity in the left superior parietal lobe, ventromedial prefrontal cortex, and posterior cingulate cortex, and altered intrinsic functional connectivity of the default mode network and salience network during visual erotic stimuli.[23 24] Resting-state fMRI studies also suggested that patients with pED not only displayed aberrant spontaneous activities at the right anterior insula but also showed abnormal connexion patterns between the right anterior insula and right dorsolateral prefrontal cortex as well as between the right anterior insula and right temporoparietal cortex. Furthermore, both the aberrant activities of the right anterior insula and the abnormal functional connexion between the right anterior insula and right temporoparietal cortex were positively correlated with participant scores on the International Index of Erectile Function (IIEF).[20 25] On structural MRI, researchers found that, when compared with healthy controls, pED sufferers presented grey matter atrophy in some subcortical structures, including the amygdala and nucleus accumbens, and the atrophied degree of left nucleus accumbens showed a close correlation with decreased erectile function.[26] Moreover, our previous study detected that patients with pED had significant microstructure alterations at the splenium of the corpus callosum and in multiple white matter regions.[27]

Based on these neuroimaging studies, we may easily conclude that pED is not only a genitourinary disease but also is associated with abnormal alterations in both brain structure and brain function. However, there is no integrated study summarising the scattered evidence of individual studies, and the central pathological alterations associated with pED remain unclear. Therefore, launching a rigorous systematic review to synthesise the hitherto existing studies is necessary to improve knowledge of the neurological underpinnings of pED and increase understanding of the role of the central nervous system in sexual activity.

Objectives

The objective of this systematic review is to integrate and assess the evidence of the impact of pED on the brain and to contribute a comprehensive summary of structural and functional brain alterations in patients with pED. This review also aims to synthesise correlations between the differences observed in some brain regions related to function or structure and the clinical characteristics of patients with pED, such as behavioural

and psychophysiological data and data obtained from disease-related scales, QoL scales and emotional scales.

METHODS

This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement[28] and has been registered at the PROSPERO International Prospective Register of Systematic Reviews of the University of York (registration number CRD42019117206).

Eligibility criteria

The inclusion and exclusion criteria of studies will be described as follows.

Study types

Case control studies, cohort studies and randomised controlled trials will be included only if the original neuroimaging data can be extracted. Case reports, narrative or systematic reviews, meta-analyses, letters and other secondhand studies will be excluded.

Study design

Neuroimaging studies centred on the differences between the brain structure, brain functional activity, and structural and functional connectivity of patients with pED and those of healthy controls will be included. Longitudinal studies focusing on the management of pED will be considered as long as the baseline neuroimaging data are reported. Both resting-state and task neuroimaging studies will be included, and no neuroimaging modality will be precluded. Any publication acquired data using multimodal neuroimaging techniques from the same participants will be collected separately in this review.[29]

Participants

Studies containing both patients with pED and parallel healthy controls will be considered for inclusion. The minimum sample size for inclusion will be restricted to 12 participants per group, according to previous studies.[29–31] The race, age and disease conditions (drug-naïve or drug-invented) of participants will not be restricted in this review.

Exposure

Patients with pED should be diagnosed by comprehensive history taking, physical examination and even specific examinations according to the diagnostic guidelines of the European Association of Urology,[32–34] the American Urological Association,[35 36] or other authoritative organisations.[37] Patients with organic ED or mixed ED or with other andrological or cardiovascular complications will be excluded. Some studies enrolling patients without clear discrimination of subtypes of ED will be considered after comprehensive full-text assessment or contact with the authors to identify the participants as patients with pED.

Comparators

Participation of a parallel healthy control group in the study is required for inclusion in the current review. Healthy controls must have no prior diagnosis of ED at enrolment, and this must be verified by clinical examination during the study. Studies absenting from healthy controls will be excluded.

Outcome measures

The primary outcomes of the included studies should be functional and structural brain alterations of the patients with pED. Brain structure outcomes are related to white matter microstructure, grey matter density or volume, or structural connectivity. Outcomes related to brain function include whole-brain or region-of-interest functional activity or functional connectivity (fMRI based on blood-oxygen-level-dependent signal or cerebral blood flow), brain molecular metabolism (positron emission tomography or single-photon emission CT); neurochemical activity (magnetic resonance spectroscopy); or brain electrical activity (electroencephalogram). The secondary outcomes of these studies may contain behavioural and psychophysiological data (such as genital responses and heart and respiratory rates)[23 24]; symptom-related scales (such as IIEF-5,[38] Quality of Erection Questionnaire[39] and the Erection Hardness Score[40]); QoL questionnaire (the Sexual Life Quality Questionnaire)[41]; or psychological assessment scales (such as the Self-Rating Anxiety Scale,[42] the Self-Rating Depression Scale[43] and the Brief Psychiatric Rating Scale[44]). Studies with only a primary outcome will also be included in this review.

Report characteristics

Peer-reviewed original studies will be included. Conference proceedings and unpublished theses will be excluded. Publication time will be restricted to prior to 1 October 2019 (the anticipated completion date of this review), and language will be restricted to English and Chinese.

Searching strategy

Electronic searching will be conducted in PubMed, EMBASE, Web of Science, China Biology Medicine Database and CNKI using medical subject headings (MeSH) terms. The searching strategies of PubMed (English) and CNKI (Chinese) are displayed in table 1 and will be replicated for the other electronic databases. Thereafter, the snowballing search strategy will be employed to find other eligible studies according to the reference lists of enrolled literature. In addition, the WHO International Clinical Trials Registry Platform will be searched for potential results.

Selection process

Covidence (https://www.covidence.org), the Cochrane Library-recommended online systematic review management system, will be used to manage literature. The initial searching results obtained following the above strategies will be uploaded to Covidence. After duplicates are

Table 1 Searching items for identifying articles in PubMed (English) and CNKI (Chinese)

PubMed searching strategy	CNKI searching strategy
#1 Erectile Dysfunction (MeSH Terms)	#1 阳痿(主题词)
#2 Impoten* (All Fields)	#2 勃起功能障碍(主题词)
#3 Erectile disturbance (All Fields)	#3 性功能障碍(主题词)
#4 Erectile disorder (All Fields)	#4 ED(主题词)
#5 Sexual Dysfunction (MeSH Terms)	#5 #1 OR #2 OR#3 OR #4
#6 Asynodia (All Fields)	#6 神经影像学(主题词)
#7 Erection failure (All Fields)	#7 功能磁共振(主题词)
#8 Penile Erection (MeSH Terms)	#8 磁共振成像(主题词)
#9 #1 OR #2 OR#3 OR #4 OR #5 OR #6 OR #7 OR #8	#9 MRI(主题词)
#10 Neuroimaging (MeSH Terms)	#10 PET(主题词)
#11 Functional Neuroimaging (MeSH Terms)	#11 SPECT(主题词)
#12 Brain imaging (All Fields)	#12 EEG(主题词)
#13 MRI (MeSH Terms)	#13 MRS(主题词)
#14 Magnetic resonance* (MeSH Terms)	#14 DTI(主题词)
#15 MRI (All Fields)	#15 #6 OR #7 OR #8 OR #9 OR #10 OR#11 OR #12 OR #13 OR #14
#16 Tomography (MeSH Terms)	**#16 Final search terms: #5 AND #15**
#17 Positron Emission Tomography (MeSH Terms)	
#18 Tomography, Emission-Computed, Single-Photon (MeSH Terms)	
#19 PET (All Fields)	
#20 PET-CT (All Fields)	
#21 Single Photon Emission CT (MeSH Terms)	
#22 SPECT (All Fields)	
#23 Electroencephalography (MeSH Terms)	
#24 EEG (All Fields)	
#25 Magnetic Resonance Spectroscopy (MeSH Terms)	
#26 MRS (All Fields)	
#27 Diffusion Tensor Imaging (MeSH Terms)	
#28 DTI (All Fields)	
#29 #10 OR#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	
#30 Final search terms: #9 AND #29	

removed, TY will screen the title and abstract to remove the obviously irrelevant records. Then two reviewers (TY and JX) will complete the abstract and full-text review in parallel. Any disagreement between TY and JX will be reconsidered by a third reviewer (ZL). In order to assess the reliability of the selection criteria and inter-rater agreement between the two reviewers, Cohen's kappa will be calculated at the parallel selection stage; a kappa coefficient (k) over 0.75 will indicate high reliability.[45]

The record selection process will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram[46] and elimination reasons for ineligible records will be reported in detail.

Data collection

The two independent reviewers (TY and JX) will doubly extract data using a standard data extraction spreadsheet in Excel. Again, any inconsistency between reviewers will be reconsidered and the result determined by ZL, the third reviewer.

The following information will be retrieved and extracted from each record.

▶ Publication information: title, first author, publishing time, country or region and funding support.

▶ Details of methodology: participants, sample size, diagnostic criteria, demographic characteristics (including age, handedness, ethnicity and education), imaging modalities, data analysis strategies, pED-related cognitive-behavioural models and clinical outcomes.

▶ Results: the significant altered cerebral regions (described by peak Montreal Neurological Institute (MNI)/Talairach coordinate, cluster size and statistical threshold); the value of clinical characteristics (behavioural and psychophysiological data, disease-related scales, QoL scales, emotional scales, etc); and the correlations between imaging data and clinical data.

Any missing information or questions about the above data will be settled by contacting the authors. If no clarification is provided after 4 weeks, the study will be included in the final analysis with the missing information marked.

Outcomes and prioritisation

The primary outcome of this review will be the significantly altered cerebral regions in patients with pED when compared with healthy controls. Due to the variety of analytical methods and great heterogeneity of the studies' statistical thresholds (e.g. voxel cluster size thresholds, statistical magnitudes, methods of correcting for multiple comparisons), it is unrealistic to set a uniform significance threshold. Therefore, the significance of results will be determined by the study authors' own criteria.[47] Some neuroimaging studies also report results trending to significant or significant only before correction.[47] For a more comprehensive view, these regions will be collected with special symbols in the qualitative synthesis. The secondary outcome of this review will be the associations between the altered cerebral structure and function and the clinical characteristics, which mainly include behavioural and psychophysiological data, disease-related scales, QoL scales, emotional scales and so on. The values of these clinical characteristics will be recorded and may be used to explain interstudy variability when necessary.

Quality assessment

There are no standardised criteria for quality assessment of neuroimaging studies.[48 49] Authors of previous systematic reviews have always developed their own quality assessment tools based on existing tools (such as QUADAS-2 and the Newcastle-Ottawa Scale (NOS)).[48 50–54] However, because of the diverse study objectives, current assessment tools are not suitable for this review. Therefore, after referring to the NOS,[55] some published systematic reviews,[48–50 56] and the Committee on Best Practices in Data Analysis and Sharing in Neuroimaging Using MRI[57] (http://www.humanbrainmapping.org), a customised checklist is proposed for the current review. This checklist will be used to evaluate the quality of the included studies based on nine items (table 2). Each item is scored as 1 (Yes) or 0 (No or Don't know), and the summation of items generates an overall quality score (0–9 points). Each study's quality is defined as high (8–9 points), medium (5–7 points), or low (0–4 points).

Quality assessment will be performed by a professional assessor (LL) who is experienced with quality assessment scoring and a nonprofessional assessor (RS) who has never engaged in quality assessment of systematic reviews. These two assessors will independently evaluate the enrolled studies based on the checklist; any discrepancy

Table 2	Checklist of quality assessment			
Quality assessment categories		**Yes**	**No**	**Don't know**
1. The study addressed an explicit question (theory-driven)				
2. With sufficient sample size or used justified power calculation				
3. With clearly inclusion criteria and exclusion criteria of participants				
4. Controlled the important confounding factors such as age, handiness and education of participants				
5. With adequate quality control during data acquisition				
6. Described the response rate in detail				
7. Assessed outcomes with blinded or third-party assessors				
8. Used appropriate multiple testing correction in statistical modelling and inference				
9. Reported detailed imaging results including MNI/Talairach coordinate, statistic magnitudes cluster sizes and statistical threshold				

will be reconsidered by the third reviewer (ZL). Again, the inter-rater agreement will be assessed by Cohen's kappa with k>0.75 indicating high reliability.

Data synthesis

The collected data, including publication information, methodologies, and significant study findings, will be summarised in a table. Methodologies and neuroimaging results will then be pooled and described in detail. The total and average sample size, age range of participants and mean duration of patients of included studies will be calculated, and the cognitive-behavioural models, outcomes of behavioural and psychophysiological measurement, disease-related scales, QoL scales, and emotional scales will be summarised. A qualitative review will be performed to synthesise the structural and functional brain alterations and correlations between these alterations and the clinical characteristics of patients with pED. For more clear presentation, these findings will be integrated separately according to task or resting design and neuroimaging modality. If feasible (if 17 or more resting-state studies are included),[58] an activation likelihood estimation meta-analysis[59 60] will be launched to quantitatively synthesise the differences in cerebral structure and function between patients with pED and healthy controls. Subgroup analyses will not be performed in this review. The strength of evidence of this review will be determined by the checklist described above.

CONCLUSION

Although neuroimaging studies have verified the existence of structural and functional brain alterations in patients with pED, the scattered neuroimaging biomarkers of pED in individual studies have not yet been summarised. Therefore, this systematic review is launched, aiming to synthesise the central pathological characteristics and the associations between the altered cerebral structure and function and the clinical characteristics of pED. The current review will be the first to synthesise the neuroimaging evidence of pED in a systematic way, to include a meta-analysis of the findings, and to assess the quality of these neuroimaging studies. This work will provide a coherent synthesis of the recent neuroimaging studies on pED and improve knowledge of the neurological underpinnings of pED.

Patient and public involvement

This is a protocol for systematic review. No patients and public were involved.

Ethics and dissemination

Ethical approval is not required as primary data will not be collected. This review will be published in a peer-reviewed journal and presented at conferences.

Contributors PZ was responsible for this study. TY, ZL and PZ conceived and designed the study. TY, ZL and JX participated in drafting the protocol and preparing

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