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Title

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

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

ABSTRACT

Introduction

Erectile dysfunction (ED) is the most common male sexual disorder which severely impact the sexual performance and quality of life of males. Previous studies had found that psychogenic ED (pED), the main subtype of ED, was more than a genitourinary disease, it also had abnormal alterations in both brain structure and function. However, the scattered neuroimaging biomarkers of pED in individual studies have yet been summarized. The objective of this systematic review is to integrate and assess the evidences of the impact of pED on male's brain structure and function.

Methods and analysis

Five databases (PubMed, EMBASE, Web of Science, CBM, CNKI) will be systematically searched from inception to 1 March 2019 with language restricted at English and Chinese. Those studies focusing on the structural and functional alterations in pED patients will be considered. The study selection will follow the PRISMA guideline and the quality assessment will be conducted with a customized checklist. A qualitative review will be performed to synthesize the brain structural and functional alterations and the correlations between these altered cerebral regions and the clinical variables in pED patients. If data available, an activity 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

Keywords

Erectile dysfunction, Neuroimaging, Magnetic resonance imaging, Activity likelihood estimation

Strengths and limitations of this study

1. This is the first systematic review and meta-analysis which integrate and assess the central pathological characteristics of pED.
2. The qualitative description and quantitative synthesis (activity likelihood estimation meta-analysis) will be combining used in this study.
3. A customized checklist is proposed to evaluate the quality of included studies according to the purpose of this review.
4. This review will not restrict the race and age of participants, which will increase the heterogeneity of included studies and may increase the risk of bias of the review.

INTRODUCTION

Erectile dysfunction (ED) is the most common male sexual disorder which characterized by the persistent inability to attain or maintain an adequate erection to obtain satisfactory sexual performance[1]. According to the epidemiological studies, approximately 37% of males over 70 years old, and 11% of males in 30 years old suffered from this sexual dysfunction[2]. As a physical and psychosocial illness, ED not only impair male sexual confidence and satisfaction, but also severely impact the quality of life (QoL)[3 4] and marital relationship[5] of patients and their female partners. More importantly, ED has been confirmed as an independent risk factor of cardiovascular diseases[6 7]. Based on the different causes[8 9], ED is classified as psychogenic ED (pED), organic ED such as arteriogenic ED, Neurogenic ED, venogenic ED, etc. and mixed ED. Different from organic ED which has clear causes and pathological features, pED is generally caused by some uncertain psychological factors[10 11] and lack specific biomarkers.

Rationale for review

Penile erection is a complex physiological process which modulated by the central

nervous system (CNS) and mediated by several neurotransmitters and neuropeptides[12 13]. A meta-analysis identified that penile erection was regulated by several cerebral regions and the activities of insular cortex, claustrum, putamen, and anterior midcingulate cortex were consistently positively correlated with male penile erection[14].

With the close relationship between brain and penile erection been wildly accepted, using neuroimaging techniques to explore the central pathological features of ED attracted many researchers' attention[15-20]. For example, a functional MRI (fMRI) studies on pED patients' sexual arousal reported that pED patients manifested deactivation in left superior parietal lobe and prefrontal cortex during neurobehavioural stimulus[21]. Another resting-state fMRI studies also suggested that aberrant connection patterns between right anterior insula and right dorsolateral prefrontal cortex as well as right anterior insula and right temporoparietal might be the highlighted neuroimaging biomarkers of pED[22]. With structural MRI, researchers found that compared with healthy controls (HCs), pED sufferers presented grey matter atrophy in some subcortical structures including amygdala and nucleus accumbens, and the atrophied degree of left nucleus accumbens have a significant correlation with low erectile function[23]. Moreover, our previous studies[24] also determined that pED patients have significant white matter microstructure alterations.

Based on these neuroimaging studies, it could easily conclude that pED was more than a genitourinary disease, it also has abnormal alterations in both brain structure and functional activity. However, there were still some inconsistent or even contradictory results in these studies because of the methodological issues, and the central pathological alterations associated with pED remain unclear. Therefore, launching a rigorous systematic review to synthesize the hitherto existing studies is necessary, it will improve our knowledge of pED's neurological underpinnings and help to understand the role of CNS in sexual activity.

Objectives

The objective of this review is to contribute a comprehensive summary of brain

structural and functional alterations in pED patients compared with the HCs. Furthermore, this review also aims to synthesize the probable correlations between these altered cerebral regions and the clinical variables.

METHODS

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement[25] and has been registered with 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 with the following items:

Types of study

The case-control studies, cohort studies, as well as randomized controlled trials will be included only if the original data of neuroimaging findings could be extracted. The case reports, narrative or systematic reviews, meta-analyses, letters, and other second-hand studies will be excluded.

Study design

Neuroimaging studies which centred on the differences in brain structure, brain functional activity, structural and functional connectivity, etc. between pED patients and HCs will be included. The longitudinal studies focusing on the management of pED will also be considered as long as the baseline neuroimaging data was reported. Both the resting state and task neuroimaging studies will be included, and no neuroimaging modality will be restricted. Any publication acquired data using multimodal neuroimaging techniques from the same participants will be collected separately in this review[26].

Participants

Participants will be limited at the definite pED patients and the age-matched HCs, and the minimum sample size is restricted at 12 participants per group according to

previous studies[26-28]. The race and age of participants will not be restricted in this review.

Exposure

pED patients should be diagnosed with comprehensive history taking, physical examination and even specific examinations according to the diagnostic guidelines of European Association of Urology (EAU)[29-31], American Urological Association (AUA)[32 33] or other authoritative organization[34]. The organic ED or mixed ED patients, or patients with other andrological or cardiovascular complications will be excluded. Some studies enrolled participants without clear discrimination of organic or psychogenic ED will be considered after the comprehensive full-text assessment or contacting the authors to identify the patients as pED.

Comparators

Containing a parallel HCs group is required for studies to be included in the current review. Studies must contain HCs who had never been diagnosed with ED before enrolment and had been reverified with the clinical examinations during researches. Studies absenting from HCs or contrasting with previous studies will be excluded.

Outcome measures

The primary outcomes of the included studies are the functional and structural alterations in the brain of the pED patients. The cerebral structure variables include white matter microstructure, gray matter density and volume, and structural connectivity. The cerebral function variables include whole-brain and region-of-interest functional activity, functional connectivity (fMRI based on blood-oxygen-level-dependent signal or cerebral blood flow), brain molecular metabolism (PET, Single-Photon Emission Computed Tomography (SPECT)), neurochemical activity (Magnetic Resonance Spectroscopy (MRS)) as well as brain electrical activity (Electroencephalogram (EEG)), etc. The secondary outcomes of these studies contain disease-related scales, QoL scales, emotional scales, and so on.

Report characteristics

The peer-reviewed original studies will be included, the conference proceedings and

unpublished theses will be excluded. The publishing time will be restricted up to 1 March 2019 and the language will be restricted at English and Chinese.

Search strategy

Electronic searching will be conducted in PubMed, EMBASE, Web of Science, China Biology Medicine Database (CBM) and China National Knowledge Infrastructure (CNKI) using the medical subject headings (MeSH) terms. The PubMed (English) and CNKI (Chinese) searching strategies are displayed in Table 1, and they will be replicated for other electronic databases. Thereafter, the snowballing searching 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 also be searched to mining more potential results.

[Insert Table 1 here]

Selection process

Covidence (https://www.covidence.org), the Cochrane Library recommend online systematic review management system, will be used to manage literature. The initial searching results with above strategies will be uploaded to Covidence for the first step. After duplicates removed, TY will screen the title and abstract to identify eligible records, JX will also randomly select 15% of records for screening to assess the inter-rater agreement of the selection criteria. In this review, all the inter-rater reliability will be assessed by kappa value. Kappa value over 0.75 indicates a high agreement[35]. After title and abstract screening completed, full-text records will be uploaded to Covidence for intensive reading. Two reviewers (TY and JX) will independently complete the full-text review, any disagreement between YT and XJ will be reconsidered by a third reviewer (ZL). In this stage, eliminated reasons will be detailed reported for those ineligible records.

The selecting process of records will be reported using the PRISMA flow diagram[36].

Data collection

Two independent reviewers (TY and JX) will doubly extract data using a standard

data extraction spreadsheet in Excel. Again, any inconsistency between these two reviewers will also be consulted and judged by ZL, the third reviewer.

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

- Publication information: title, first author, publishing time, country/region, funding supports.
- Details of methodology: participants, sample size, diagnostic criteria, demographic characteristics (including age, handedness, ethnicity, and education), imaging modalities, data analysis strategies, and clinical outcome measures.
- Results: the significant altered cerebral regions (described with peak MNI/Talairach coordinate, cluster sizes, and statistical threshold) and the correlations of imaging data and clinical data.

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

Outcomes and prioritization

The primary outcome of this review is the significant altered cerebral regions in pED patients compared with HCs. However, due to the variety of analytical measures employed and great heterogeneity of the statistical thresholds of each study (e.g. voxel cluster size thresholds, statistic magnitudes, methods of correcting for multiple comparisons), it is unrealistic to set a uniform significance threshold. Therefore, the 'significant' results will follow the study authors' own criteria[37]. Some neuroimaging studies also reported results trending to significance or significant results only before correction[37], for a more comprehensive view, these regions will be collected with special symbols in qualitative synthesis. The secondary outcome is the correlations of abnormal cerebral regions and clinical variables, which mainly include symptom-related scales (such as International Index of Erectile Function 5 (IIEF-5)[38], Quality of Erection Questionnaire (QEQ)[39], and the Erection Hardness Score (EHS))[40], QoL questionnaire (the Sexual Life Quality Questionnaire (SLQQ))[41] and

psychological assessment scales (such as Self-Rating Anxiety Scale (SAS)[42], Self-Rating Depression Scale (SDS)[43], and Brief Psychiatric Rating Scale (BPRS)[44]).

Quality assessment

There are no standardized criteria for quality assessment of neuroimaging studies[45 46]. Researchers of each study developed their own assessment tools based on some existing tools (such as QUADAS-2, Newcastle-Ottawa Scale (NOS))[45 47-51]. However, because of the diverse objects of studies, the currently existing assessment tools are not very suitable for our review. Therefore, after referring the NOS[52], some published systematic reviews[45-47 53] and the Committee on Best Practices in Data Analysis and Sharing in Neuroimaging Using MRI[54] (http://www.humanbrainmapping.org), a customized checklist is proposed in the current review. This checklist will be used to evaluate the quality of the enrolled studies from 9 items (Table 2). Each item is scored as 1 (Yes) or 0 (No or Don't know), and the summation of each item generates an overall quality score. The quality levels of studies are defined as high (8–9 points), medium (5–7points) and low (1–4 points).

[Insert Table 2 here]

Quality assessment will be performed by a professional assessor (LL) and a non-professional assessor (RS). These two assessors will independently evaluate the enrolled studies based on the checklist, any discrepancy will also be reconsidered by a third reviewer (ZL). Again, the inter-rater reliability will be assessed by kappa value.

Data Synthesis

Firstly, collected data including publication information, methodology, and the significant findings of studies will be summarized with a table. And then, a qualitative review will be performed to synthesize the brain structural and functional alterations and the correlations between these altered cerebral regions and the clinical variables in pED patients. If feasible (17 or more studies are included[55]), an activity likelihood estimation meta-analysis[56 57] will also be launched to quantitatively synthesize the differences of cerebral structure and function between pED patients and HCs. The

subgroup analyses will not be performed in this review. The strength of evidence for the final conclusion will be determined by the checklist described above.

CONCLUSION

Neuroimaging studies have verified the existence of structural and functional alterations in the brain of pED patients, while the scattered neuroimaging biomarkers of pED in individual studies have yet been summarized. Therefore, this systematic review will be launched, aiming to synthesize the central pathological characteristics of pED for the first time. This work will provide a coherent synthesis of the recent neuroimaging studies on pED and improve our knowledge of pED's neurological underpinnings.

Patient and public involvement

This is a systematic review protocol; no patients and public were involved.

Ethics and dissemination

Ethical approval is not required for this study. This review will be published in a peer-reviewed journal and presented at conferences.

Contributors

Peihai Zhang was responsible for this study. Tao Yin, Zhengjie Li and Peihai Zhang conceived and designed the study. Tao Yin, Zhengjie Li and Jing Xiong participated in drafting the trial protocol and preparing the manuscript. Lei Lan, Ruirui Sun and Feiqiang Ren provided feedback on the study design and protocol. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient consent

Not required.

Data sharing statement

This paper does not include original data.

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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 [ ]
#2 Impoten* [All Fields]	#2 [ ]
#3 Erectile disturbance [All Fields]	#3 [ ]
#4 Erectile disorder [All Fields]	#4 ED [ ]
#5 Sexual Dysfunction [MeSH Terms]	#5 #1 OR #2 OR#3 OR #4
#6 Asynodia [All Fields]	#6 [ ]
#7 Erection failure [All Fields]	#7 [ ]
#8 Penile Erection [MeSH Terms]	#8 [ ]
#9 #1 OR #2 OR#3 OR #4 OR #5 OR #6 OR #7	#9 MRI [ ]
OR #8	#10 PET [ ]
#10 Neuroimaging [MeSH Terms]	#11 SPECT [ ]
#11 Functional Neuroimaging [MeSH Terms]	#12 EEG [ ]
#12 Brain imaging [All Fields]	#13 MRS [ ]
#13 Magnetic resonance imaging [MeSH Terms]	#14 DTI [ ]
#14 Magnetic resonance* [MeSH Terms]	#15 #6 OR #7 OR #8 OR #9 OR #10
#15 MRI [All Fields]	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 Computed Tomography [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 #9 OR #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	
#30 Final search terms: #9 AND #29	

Table 2. The 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.			

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Line 3, Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Line 27, Page 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Line 15, Page 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Line 21, Page 10
Sponsor	5b	Provide name for the review funder and/or sponsor	Line 21, Page 10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Line 21, Page 10
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Line 27, Page 3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Line 28, Page 4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report	Line 9, Page 5

		characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Line 4, Page 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1, Page 15
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Line 14, Page 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Line 13, Page 7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Line 27, Page 7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Line 3, Page 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Line 16, Page 8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Not applicable
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Line 26, Page 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's (□	Line 26, Page 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Line 28, Page 9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Line 22, Page 9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective	Not applicable

		reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Line 3, Page 9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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

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Title page

Title

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

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

ABSTRACT

Introduction

Erectile dysfunction (ED) is the most common male sexual disorder which severely impacts the sexual performance and quality of life of men. As the main subtype of ED, psychogenic ED (pED) has been demonstrated that not only was a genitourinary disease, but also had alterations in both brain structure and function. However, those scattered neuroimaging evidence in individual studies have 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 men's brain structure and function.

Methods and analysis

Five databases (PubMed, EMBASE, Web of Science, China Biology Medicine Database, China National Knowledge Infrastructure) will be systematically searched from inception to 1 October 2019 (the anticipated completion date of this review) with language restricted at English and Chinese. Those studies focusing on the structural or functional alterations in patients with pED will be retrieved. The study selection process will follow the PRISMA guideline and the quality assessment will be conducted with a customized checklist. After data extraction, a qualitative review will be performed to synthesize the brain structural and functional alterations as well as the correlations between these altered cerebral structure /function and the clinical characters in patients with pED. If data feasible, an activity 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

Keywords

Psychogenic erectile dysfunction, Neuroimaging, Magnetic resonance imaging, Activity likelihood estimation

Strengths and limitations of this study

1. This is the first systematic review and meta-analysis which integrate and assess the central pathological characters of pED.
2. The qualitative and quantitative synthesis (activity likelihood estimation meta-analysis) will be combining used in this study.
3. A customized checklist is proposed to evaluate the quality of the included studies according to the purpose of this review.
4. This review does not restrict the race, age, and disease conditions of participants and detailed pre-processing procedures of included studies, which will increase the heterogeneity of included studies and may increase the risk of bias of the review.

INTRODUCTION

Erectile dysfunction (ED) is the most common male sexual disorder which characterized 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 the epidemiological studies, approximately 37% of men over 70 years old, and 11% of men in 30 years old suffered from this sexual 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 marital relationship[7] of patients and their female partners. More importantly, ED has been increasingly regarded as an independent risk factor of cardiovascular diseases[8 9]. According to the 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 characters, pED is generally caused by some uncertain psychological

factors[12 13] and lacks specific biomarkers.

Rationale for review

Penile erection is a complex physiological process which was modulated by the central nervous system (CNS) and mediated by several neurotransmitters and neuropeptides[14 15]. A meta-analysis identified that penile erection was regulated by several cerebral regions; and the activities of insular cortex, claustrum, putamen, and anterior midcingulate cortex were consistently positively correlated with male penile erection[16]. With the close relationship between brain and penile erection being wildly accepted, using neuroimaging techniques to explore the central pathological characters of pED attracted many researchers' attention[17-22]. For example, two task functional MRI (fMRI) studies focusing on male sexual arousal reported that compared with healthy controls, patients with pED manifested lower penile tumescence, larger activities in left superior parietal lobe, ventromedial prefrontal cortex and posterior cingulate cortex, as well as altered intrinsic functional connectivity at 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 connection patterns between right anterior insula and right dorsolateral prefrontal cortex as well as right anterior insula and right temporoparietal; furthermore, both the aberrant activities at right anterior insula and the abnormal functional connection between right anterior insula and right temporoparietal were positively correlated with the scores of International Index of Erectile Function (IIEF) scale in participants[25 26]. With structural MRI, researchers found that compared with healthy controls, pED sufferers presented grey matter atrophy in some subcortical structures including amygdala and nucleus accumbens, and the atrophied degree of left nucleus accumbens showed a close correlation with patients' decreased erectile function[27]. Moreover, our previous study[28] also detected that patients with pED had significant microstructure alterations at splenium of the corpus callosum and multiple white matter regions.

Based on these neuroimaging studies, we could easily conclude that pED not only was

a genitourinary disease, but also had abnormal alterations in both brain structure and function. However, there is still no integrated study to summarize the scattered evidence in individual studies, and the central pathological alterations associated with pED remain unclear. Therefore, launching a rigorous systematic review to synthesize the hitherto existing studies is necessary, which will improve our knowledge to the neurological underpinnings of pED and help to better understand the role of CNS in sexual activity.

Objectives

The objective of this systematic review is to integrate and assess the evidence of the impact of pED on men's brain and to contribute a comprehensive summary of brain structural and functional alterations in patients with pED. Furthermore, this review also aims to synthesize the probable associations between the statistical differences observed in some brain regions regarding the function or structure and the clinical characters such as behavioural /psychophysiological data, disease-related scales, QoL scales, and emotional scales in patients with pED.

METHODS

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement[29] 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 with the following items:

Types of study

The case-control studies, cohort studies, as well as randomized controlled trials will be included only if the original data of neuroimaging findings could be extracted. The case reports, narrative or systematic reviews, meta-analyses, letters, and other second-hand studies will be excluded.

Study design

Neuroimaging studies which centred on the differences of brain structure, brain functional activity, structural and functional connectivity, etc. between patients with pED and healthy controls will be included. The longitudinal studies focusing on the management of pED will also be considered as long as the baseline neuroimaging data were reported. Both the resting-state and task neuroimaging studies will be included, and no neuroimaging modality will be restricted. Any publication acquired data using multimodal neuroimaging techniques from the same participants will be collected separately in this review[30].

Participants

Participants will be limited at the clearly diagnosed patients with pED and the parallel healthy controls. The minimum sample size for inclusion is restricted at 12 participants per group according to previous studies[30-32]. 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 with comprehensive history taking, physical examinations and even specific examinations according to the diagnostic guidelines of European Association of Urology (EAU)[33-35], American Urological Association (AUA)[36 37] or other authoritative organizations[38]. The organic ED or mixed ED, or patients with other andrological or cardiovascular complications will be excluded. Some studies enrolling patients without clear discrimination of subtypes of ED will be considered after the comprehensive full-text assessment or contacting the authors to identify the patients as pED.

Comparators

Containing the parallel healthy control group is required for studies to be included in the current review. Healthy controls in those studies should never be diagnosed with ED before enrolment and had been reverified with the clinical examinations during researches. Studies absenting from healthy controls or contrasting with previous studies will be excluded.

Outcome measures

The primary outcomes of the included studies should be the functional and structural alterations in the brain of the patients with pED. The outcomes of brain structure include white matter microstructure, gray matter density and volume, and structural connectivity. The outcomes of brain function include whole-brain /region-of-interest functional activity, functional connectivity (fMRI based on blood-oxygen-level-dependent (BOLD) signal or cerebral blood flow), brain molecular metabolism (Positron Emission Tomography (PET), Single-Photon Emission Computed Tomography (SPECT)), neurochemical activity (Magnetic Resonance Spectroscopy (MRS)) as well as brain electrical activity (Electroencephalogram (EEG)), etc. The secondary outcomes of these studies may contain behavioural /psychophysiological data (such as genital responses, heart and respiratory rates[23 24]), symptom-related scales (such as IIEF-5[39], Quality of Erection Questionnaire (QEQ)[40], and the Erection Hardness Score (EHS))[41], QoL questionnaire (the Sexual Life Quality Questionnaire (SLQQ))[42] and psychological assessment scales (such as Self-Rating Anxiety Scale (SAS)[43], Self-Rating Depression Scale (SDS)[44], and Brief Psychiatric Rating Scale (BPRS)[45]). Studies only have primary outcome will also be included in this review.

Report characteristics

The peer-reviewed original studies will be included, the conference proceedings and unpublished theses will be excluded. The publishing time will be restricted up to 1 October 2019 (the anticipated completion date of this review) and the language will be restricted at English and Chinese.

Searching strategy

Electronic searching will be conducted in PubMed, EMBASE, Web of Science, China Biology Medicine Database (CBM) and China National Knowledge Infrastructure (CNKI) using the medical subject headings (MeSH) terms. The searching strategies of PubMed (English) and CNKI (Chinese) are displayed in Table 1 and will be replicated for other electronic databases. Thereafter, the snowballing searching 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 also be searched to mining more potential results.

[Insert Table 1 here]

Selection process

Covidence (https://www.covidence.org), the Cochrane Library recommend online systematic review management system, will be used to manage literature. The initial searching results with the above strategies will be uploaded to Covidence. After duplicates removed, TY will screen the title and abstract to remove the obviously irrelevant records; and then, the two reviewers (TY and JX) will parallelly complete the abstract and full-text review. 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 the inter-rater agreement between the two reviewers, the Cohen's Kappa will be calculated at the parallel selection stage, and the Kappa coefficient (k) over 0.75 indicates high reliability[46]. The selection process of records will be reported using the PRISMA flow diagram[47] and the eliminated reasons for those ineligible records will be detailed reported.

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 these two reviewers will also be consulted and judged by ZL, the third reviewer.

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

- Publication information: title, first author, publishing time, country /region, funding supports.
- Details of methodology: participants, sample size, diagnostic criteria, demographic characteristics (including age, handedness, ethnicity, and education), imaging modalities, data analysis strategies, and clinical outcomes.
- Results: the significant altered cerebral regions (described with peak MNI

/Talairach coordinate, cluster size, and statistical threshold), the value of clinical characters (behavioural /psychophysiological data, disease-related scales, QoL scales, emotional scales, etc.), and the correlations between imaging data and clinical data.

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

Outcomes and prioritization

The primary outcome of this review is the significant altered cerebral regions in patients with pED compared with healthy controls. Due to the variety of analytical methods and great heterogeneity of the statistical thresholds of studies (e.g. voxel cluster size thresholds, statistic magnitudes, methods of correcting for multiple comparisons), it is unrealistic to set a uniform significance threshold. Therefore, the 'significant' results will follow the study authors' own criteria[48]. Some neuroimaging studies also reported results trending to significant or significant only before correction[48]. For a more comprehensive view, these regions will be collected with special symbols in the qualitative synthesis. The secondary outcome of this review is the associations of the altered cerebral structure /function and the clinical characters which mainly include behavioural /psychophysiological data, disease-related scales, QoL scales, emotional scales, and so on. The values of these clinical characters will be recorded, and they might be used to explain the inter-studies variability when necessary.

Quality assessment

There are no standardized criteria for quality assessment of neuroimaging studies[49 50]. Authors of the previous systematic reviews always developed their own quality assessment tools based on some existing tools (such as QUADAS-2, Newcastle-Ottawa Scale (NOS))[49 51-55]. However, because of the diverse objects of studies, the currently existing assessment tools are not very suitable for our review. Therefore, after referring the NOS[56], some published systematic reviews[49-51 57] and the Committee on Best

Practices in Data Analysis and Sharing in Neuroimaging Using MRI[58] (http://www.humanbrainmapping.org), a customized checklist is proposed in the current review. This checklist will be used to evaluate the quality of the included studies from 9 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). The quality levels of studies are defined as high (8–9 points), medium (5–7points) and low (0–4 points).

[Insert Table 2 here]

Quality assessment will be performed by a professional assessor (LL) who is experienced with quality assessment scoring and a non-professional assessor (RS) who have never engaged in quality assessment of systematic reviews. These two assessors will independently evaluate the enrolled studies based on the checklist; any discrepancy will also be reconsidered by the third reviewer (ZL). Again, the inter-rater agreement will be assessed by Cohen's Kappa with the threshold k>0.75 indicating high reliability.

Data Synthesis

Firstly, collected data including publication information, methodologies, and the significant findings of studies will be summarized with a table. And then, a qualitative review will be performed to synthesize the brain structural and functional alterations and the correlations between these altered cerebral structure/ function and the clinical characters in patients with pED. For a clearer presentation, these findings will be integrated separately according to the task /resting design and neuroimaging modalities. If feasible (17 or more resting-state studies are included[59]), an activity likelihood estimation meta-analysis[60 61] will be launched to quantitatively synthesize the differences of cerebral structure and function between patients with pED and healthy controls. The subgroup analyses will not be performed in this review. The strength of evidence for the final conclusion of this review will be determined by the checklist described above.

CONCLUSION

While neuroimaging studies have verified the existence of brain structural and functional alterations in patients with pED, the scattered neuroimaging biomarkers of pED in individual studies have yet been summarized. Therefore, this systematic review is launched, aiming to synthesize the central pathological characters and the associations between the altered brain structure /function and clinical characters of pED. The current review will be the first to synthesize the neuroimaging evidence of pED in a systematic way, to include a meta-analysis of the findings, and the first to assess the quality of these neuroimaging studies. This work will provide a coherent synthesis of the recent neuroimaging studies on pED and improve our knowledge to 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 for this study. This review will be published in a peer-reviewed journal and presented at conferences.

Contributors

Peihai Zhang was responsible for this study. Tao Yin, Zhengjie Li and Peihai Zhang conceived and designed the study. Tao Yin, Zhengjie Li and Jing Xiong participated in drafting the protocol and preparing the manuscript. Lei Lan, Ruirui Sun and Feiqiang Ren provided feedback on the study design and protocol. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient consent

Not required.

Data sharing statement

This paper does not include the original data.

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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 Magnetic resonance imaging [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 Computed Tomography [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	

Table 2. The 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.			

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Line 3, Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Line 2, Page 3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Line 10, Page 11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Line 16, Page 11
Sponsor	5b	Provide name for the review funder and/or sponsor	Line 16, Page 11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Line 16, Page 11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Line 1, Page 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Line 7, Page 5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report	Line 20, Page 5

		characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Line 4, Page 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1, Page 16
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Line 4, Page 8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Line 3, Page 8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Line 16, Page 8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Line 20, Page 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Line 5, Page 9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Not applicable
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Line 12, Page 10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Line 12, Page 10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Line 20, Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Line 17, Page 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective	Not applicable

		reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Line 19, Page 9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Primary Subject Heading:	Sexual health
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Title page

Title

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

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

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) 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 PRISMA guideline and quality assessment will be conducted with a customized checklist. After data extraction, a qualitative review will be performed to synthesize 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

Keywords

Psychogenic erectile dysfunction, Neuroimaging, Magnetic resonance imaging, Activation likelihood estimation

Strengths and limitations of this study

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

INTRODUCTION

Erectile dysfunction (ED) is the most common male sexual disorder. It is characterized 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 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 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 magnetic resonance imaging (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 connection 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 connection between the right anterior insula and right temporoparietal cortex were positively correlated with participant scores on the International Index of Erectile Function (IIEF) .[25 26] 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.[27] 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.[28]

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 summarizing the scattered evidence of individual studies, and the central pathological alterations associated with pED remain unclear. Therefore, launching a rigorous systematic review to synthesize 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 synthesize 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 Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement[29] 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 randomized 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 second-hand 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.[30]

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.[30-32] 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 (EAU)[33-35], the American Urological Association (AUA)[36 37], or other authoritative organizations[38]. 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 computed tomography); 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[39], Quality of Erection Questionnaire (QEQ)[40], and the Erection Hardness Score (EHS))[41]; QoL questionnaire (the Sexual Life Quality Questionnaire (SLQQ))[42]; or psychological assessment scales (such as the Self-Rating Anxiety Scale (SAS)[43], the Self-Rating Depression Scale (SDS)[44], and the Brief Psychiatric Rating Scale (BPRS)[45]). 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 China National Knowledge Infrastructure (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.

[Insert Table 1 here]

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 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.[46] The record selection process will be reported using the PRISMA flow diagram[47] 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 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 prioritization

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.[48] Some neuroimaging studies also report results trending to significant or significant only before correction.[48] 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 standardized criteria for quality assessment of neuroimaging studies.[49 50] 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)).[49 51-55] However, because of the diverse study objectives, current assessment tools are not suitable for this review. Therefore, after referring to the NOS[56], some published systematic reviews,[49-51 57] and the Committee on Best Practices in Data Analysis and Sharing in Neuroimaging Using MRI[58] (http://www.humanbrainmapping.org), a customized checklist is proposed for the current review. This checklist will be used to evaluate the quality of the included studies

based on 9 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 (5–7points), or low (0–4 points).

[Insert Table 2 here]

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 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 summarized 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 summarized. A qualitative review will be performed to synthesize 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[59]), an activation likelihood estimation meta-analysis[60 61] will be launched to quantitatively synthesize 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 summarized. Therefore, this systematic review is launched, aiming to synthesize 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 synthesize 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

Peihai Zhang was responsible for this study. Tao Yin, Zhengjie Li and Peihai Zhang conceived and designed the study. Tao Yin, Zhengjie Li and Jing Xiong participated in drafting the protocol and preparing the manuscript. Lei Lan, Ruirui Sun and Feiqiang Ren provided feedback on the study design and protocol. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient consent

Not required.

Data sharing statement

This paper does not include the original data.

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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 Magnetic resonance imaging [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 Computed Tomography [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	

Table 2. The 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.			

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Line 3, Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Line 29, Page 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Line 13, Page 11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Line 20, Page 11
Sponsor	5b	Provide name for the review funder and/or sponsor	Line 20, Page 11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Line 20, Page 11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Line 28, Page 3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Line 8, Page 5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report	Line 21, Page 5

		characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Line 21, Page 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1, Page 16
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Line 4, Page 8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Line 2, Page 8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Line 14, Page 8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Line 18, Page 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Line 4, Page 9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Not applicable
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Line 10, Page 10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Line 10, Page 10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Line 24, Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Line 21, Page 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective	Not applicable

		reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Line 19, Page 9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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