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

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5 **1 Title page**

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8 **2 Title**

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10 Neuroimaging biomarkers of psychogenic erectile dysfunction: protocol for a
11 systematic review
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14 **5 Authors and Affiliations**

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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

1 **Keywords**

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

4 **Strengths and limitations of this study**

5 1. This is the first systematic review and meta-analysis which integrate and assess the
6 central pathological characteristics of pED.

7 2. The qualitative description and quantitative synthesis (activity likelihood estimation
8 meta-analysis) will be combining used in this study.

9 3. A customized checklist is proposed to evaluate the quality of included studies
10 according to the purpose of this review.

11 4. This review will not restrict the race and age of participants, which will increase the
12 heterogeneity of included studies and may increase the risk of bias of the review.

13 **INTRODUCTION**

14 Erectile dysfunction (ED) is the most common male sexual disorder which
15 characterized by the persistent inability to attain or maintain an adequate erection to
16 obtain satisfactory sexual performance¹. According to the epidemiological studies,
17 approximately 37% of males over 70 years old, and 11% of males in 30 years old
18 suffered from this sexual dysfunction². As a physical and psychosocial illness, ED not
19 only impair male sexual confidence and satisfaction, but also severely impact the
20 quality of life (QoL)^{3 4} and marital relationship⁵ of patients and their female partners.
21 More importantly, ED has been confirmed as an independent risk factor of
22 cardiovascular diseases^{6 7}. Based on the different causes^{8 9}, ED is classified as
23 psychogenic ED (pED), organic ED such as arteriogenic ED, Neurogenic ED,
24 venogenic ED, etc. and mixed ED. Different from organic ED which has clear causes
25 and pathological features, pED is generally caused by some uncertain psychological
26 factors^{10 11} and lack specific biomarkers.

27 **Rationale for review**

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

1 nervous system (CNS) and mediated by several neurotransmitters and neuropeptides¹²
2 ¹³. A meta-analysis identified that penile erection was regulated by several cerebral
3 regions and the activities of insular cortex, claustrum, putamen, and anterior
4 midcingulate cortex were consistently positively correlated with male penile
5 erection¹⁴.

6 With the close relationship between brain and penile erection been widely accepted,
7 using neuroimaging techniques to explore the central pathological features of ED
8 attracted many researchers' attention¹⁵⁻²⁰. For example, a functional MRI (fMRI)
9 studies on pED patients' sexual arousal reported that pED patients manifested
10 deactivation in left superior parietal lobe and prefrontal cortex during
11 neurobehavioural stimulus²¹. Another resting-state fMRI studies also suggested that
12 aberrant connection patterns between right anterior insula and right dorsolateral
13 prefrontal cortex as well as right anterior insula and right temporoparietal might be
14 the highlighted neuroimaging biomarkers of pED²². With structural MRI, researchers
15 found that compared with healthy controls (HCs), pED sufferers presented grey
16 matter atrophy in some subcortical structures including amygdala and nucleus
17 accumbens, and the atrophied degree of left nucleus accumbens have a significant
18 correlation with low erectile function²³. Moreover, our previous studies²⁴ also
19 determined that pED patients have significant white matter microstructure alterations.
20 Based on these neuroimaging studies, it could easily conclude that pED was more
21 than a genitourinary disease, it also has abnormal alterations in both brain structure
22 and functional activity. However, there were still some inconsistent or even
23 contradictory results in these studies because of the methodological issues, and the
24 central pathological alterations associated with pED remain unclear. Therefore,
25 launching a rigorous systematic review to synthesize the hitherto existing studies is
26 necessary, it will improve our knowledge of pED's neurological underpinnings and
27 help to understand the role of CNS in sexual activity.

28 **Objectives**

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

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

4 **METHODS**

5 This protocol follows the Preferred Reporting Items for Systematic Reviews and
6 Meta-Analysis Protocols (PRISMA-P) 2015 statement²⁵ and has been registered with
7 the PROSPERO International Prospective Register of Systematic Reviews of the
8 University of York (registration number: CRD42019117206).

9 **Eligibility criteria**

10 The inclusion and exclusion criteria of studies will be described with the following
11 items:

12 *Types of study*

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

17 *Study design*

18 Neuroimaging studies which centred on the differences in brain structure, brain
19 functional activity, structural and functional connectivity, etc. between pED patients
20 and HCs will be included. The longitudinal studies focusing on the management of
21 pED will also be considered as long as the baseline neuroimaging data was reported.
22 Both the resting state and task neuroimaging studies will be included, and no
23 neuroimaging modality will be restricted. Any publication acquired data using
24 multimodal neuroimaging techniques from the same participants will be collected
25 separately in this review²⁶.

26 *Participants*

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

1 previous studies²⁶⁻²⁸. The race and age of participants will not be restricted in this
2 review.

3 ***Exposure***

4 pED patients should be diagnosed with comprehensive history taking, physical
5 examination and even specific examinations according to the diagnostic guidelines
6 of European Association of Urology (EAU)²⁹⁻³¹, American Urological Association
7 (AUA)^{32 33} or other authoritative organization³⁴. The organic ED or mixed ED
8 patients, or patients with other andrological or cardiovascular complications will be
9 excluded. Some studies enrolled participants without clear discrimination of organic
10 or psychogenic ED will be considered after the comprehensive full-text assessment
11 or contacting the authors to identify the patients as pED.

12 ***Comparators***

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

17 ***Outcome measures***

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

28 ***Report characteristics***

29 The peer-reviewed original studies will be included, the conference proceedings and
30

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

3 **Search strategy**

4 Electronic searching will be conducted in PubMed, EMBASE, Web of Science, China
5 Biology Medicine Database (CBM) and China National Knowledge Infrastructure
6 (CNKI) using the medical subject headings (MeSH) terms. The PubMed (English)
7 and CNKI (Chinese) searching strategies are displayed in Table 1, and they will be
8 replicated for other electronic databases. Thereafter, the snowballing searching
9 strategy will be employed to find other eligible studies according to the reference lists
10 of enrolled literature. In addition, the WHO International Clinical Trials Registry
11 Platform will also be searched to mining more potential results.

12 [Insert Table 1 here]

13 **Selection process**

14 Covidence (<https://www.covidence.org>), the Cochrane Library recommend online
15 systematic review management system, will be used to manage literature. The initial
16 searching results with above strategies will be uploaded to Covidence for the first
17 step. After duplicates removed, TY will screen the title and abstract to identify
18 eligible records, JX will also randomly select 15% of records for screening to assess
19 the inter-rater agreement of the selection criteria. In this review, all the inter-rater
20 reliability will be assessed by kappa value. Kappa value over 0.75 indicates a high
21 agreement³⁵. After title and abstract screening completed, full-text records will be
22 uploaded to Covidence for intensive reading. Two reviewers (TY and JX) will
23 independently complete the full-text review, any disagreement between YT and XJ
24 will be reconsidered by a third reviewer (ZL). In this stage, eliminated reasons will be
25 detailed reported for those ineligible records.

26 The selecting process of records will be reported using the PRISMA flow diagram³⁶.

27 **Data collection**

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

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

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

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

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

16 **Outcomes and prioritization**

17 The primary outcome of this review is the significant altered cerebral regions in pED
18 patients compared with HCs. However, due to the variety of analytical measures
19 employed and great heterogeneity of the statistical thresholds of each study (e.g. voxel
20 cluster size thresholds, statistic magnitudes, methods of correcting for multiple
21 comparisons), it is unrealistic to set a uniform significance threshold. Therefore, the
22 ‘significant’ results will follow the study authors’ own criteria³⁷. Some neuroimaging
23 studies also reported results trending to significance or significant results only before
24 correction³⁷, for a more comprehensive view, these regions will be collected with
25 special symbols in qualitative synthesis. The secondary outcome is the correlations of
26 abnormal cerebral regions and clinical variables, which mainly include
27 symptom-related scales (such as International Index of Erectile Function 5 (IIEF-5)³⁸,
28 Quality of Erection Questionnaire (QEQ)³⁹, and the Erection Hardness Score
29 (EHS))⁴⁰, QoL questionnaire (the Sexual Life Quality Questionnaire (SLQQ))⁴¹ and
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4 1 psychological assessment scales (such as Self-Rating Anxiety Scale (SAS)⁴²,
5 2 Self-Rating Depression Scale (SDS)⁴³, and Brief Psychiatric Rating Scale (BPRS)⁴⁴).

3 **Quality assessment**

4 There are no standardized criteria for quality assessment of neuroimaging studies^{45 46}.
5 Researchers of each study developed their own assessment tools based on some
6 existing tools (such as QUADAS-2, Newcastle-Ottawa Scale (NOS))^{45 47-51}. However,
7 because of the diverse objects of studies, the currently existing assessment tools are
8 not very suitable for our review. Therefore, after referring the NOS⁵², some published
9 systematic reviews^{45-47 53} and the Committee on Best Practices in Data Analysis and
10 Sharing in Neuroimaging Using MRI⁵⁴ (<http://www.humanbrainmapping.org>), a
11 customized checklist is proposed in the current review. This checklist will be used to
12 evaluate the quality of the enrolled studies from 9 items (Table 2). Each item is scored
13 as 1 (Yes) or 0 (No or Don't know), and the summation of each item generates an
14 overall quality score. The quality levels of studies are defined as high (8–9 points),
15 medium (5–7points) and low (1–4 points).

16 [Insert Table 2 here]

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

21 **Data Synthesis**

22 Firstly, collected data including publication information, methodology, and the
23 significant findings of studies will be summarized with a table. And then, a qualitative
24 review will be performed to synthesize the brain structural and functional alterations
25 and the correlations between these altered cerebral regions and the clinical variables
26 in pED patients. If feasible (17 or more studies are included⁵⁵), an activity likelihood
27 estimation meta-analysis^{56 57} will also be launched to quantitatively synthesize the
28 differences of cerebral structure and function between pED patients and HCs. The

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

3 **CONCLUSION**

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

11 **Patient and public involvement**

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

13 **Ethics and dissemination**

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

16 **Contributors**

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

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24 China (NO.81774137).

25 **Competing interests**

26 The authors declare that they have no competing interests.

27 **Patient consent**

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4 1 Not required.

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6 **2 Data sharing statement**

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8 3 This paper does not include original data.

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1 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 OR #8	#9 MRI [] #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 OR#11 OR #12 OR #13 OR #14
#15 MRI [All Fields]	
#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	

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1 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, handedness, 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.			

2

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 τ)	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

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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.

BMJ Open

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

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Primary Subject Heading:	Sexual health
Secondary Subject Heading:	Urology
Keywords:	Neuroimaging, Magnetic resonance imaging < RADIOLOGY & IMAGING, Activity likelihood estimation, Psychogenic erectile dysfunction

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5 **1 Title page**

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8 **2 Title**

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10 Neuroimaging biomarkers of psychogenic erectile dysfunction: protocol for a
11 systematic review
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1 **Neuroimaging biomarkers of psychogenic erectile dysfunction:** 2 **protocol for a systematic review**

3 **ABSTRACT**

4 **Introduction**

5 Erectile dysfunction (ED) is the most common male sexual disorder which severely
6 impacts the sexual performance and quality of life of men. As the main subtype of
7 ED, psychogenic ED (pED) has been demonstrated that not only was a genitourinary
8 disease, but also had alterations in both brain structure and function. However, those
9 scattered neuroimaging evidence in individual studies have yet been integrated and
10 the central pathological alterations associated with pED remain unclear. The objective
11 of this systematic review is to integrate and assess the evidence of the impact of pED
12 on men's brain structure and function.

13 **Methods and analysis**

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

25 **Ethics and dissemination**

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

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4 **1 PROSPERO registration number**

5
6 2 CRD42019117206

7
8 **3 Keywords**

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10 4 Psychogenic erectile dysfunction, Neuroimaging, Magnetic resonance imaging,
11
12 5 Activity likelihood estimation

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14 **6 Strengths and limitations of this study**

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16
17 7 1. This is the first systematic review and meta-analysis which integrate and assess the
18
19 8 central pathological characters of pED.

20
21 9 2. The qualitative and quantitative synthesis (activity likelihood estimation meta-
22
23 10 analysis) will be combining used in this study.

24
25 11 3. A customized checklist is proposed to evaluate the quality of the included studies
26
27 12 according to the purpose of this review.

28
29 13 4. This review does not restrict the race, age, and disease conditions of participants and
30
31 14 detailed pre-processing procedures of included studies, which will increase the
32
33 15 heterogeneity of included studies and may increase the risk of bias of the review.

34
35 **16 INTRODUCTION**

36
37 17 Erectile dysfunction (ED) is the most common male sexual disorder which
38
39 18 characterized by the persistent inability to attain or maintain an adequate erection to
40
41 19 obtain satisfactory sexual intercourse regardless of the capability of ejaculation¹⁻³.

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43 20 According to the epidemiological studies, approximately 37% of men over 70 years
44
45 21 old, and 11% of men in 30 years old suffered from this sexual dysfunction⁴. As a
46
47 22 physical and psychosocial illness, ED not only impairs male sexual confidence and
48
49 23 satisfaction, but also severely impacts the quality of life (QoL)^{5 6} and marital
50
51 24 relationship⁷ of patients and their female partners. More importantly, ED has been
52
53 25 increasingly regarded as an independent risk factor of cardiovascular diseases^{8 9}.

54
55 26 According to the different causes^{10 11}, ED is subdivided into psychogenic ED (pED),
56
57 27 organic ED and mixed ED. Different from organic ED which has clear causes and
58
59 28 pathological characters, pED is generally caused by some uncertain psychological
60

1 factors^{12 13} and lacks specific biomarkers.

2 **Rationale for review**

3 Penile erection is a complex physiological process which was modulated by the central
4 nervous system (CNS) and mediated by several neurotransmitters and neuropeptides¹⁴
5 ¹⁵. A meta-analysis identified that penile erection was regulated by several cerebral
6 regions; and the activities of insular cortex, claustrum, putamen, and anterior
7 midcingulate cortex were consistently positively correlated with male penile erection¹⁶.

8 With the close relationship between brain and penile erection being widely accepted,
9 using neuroimaging techniques to explore the central pathological characters of pED
10 attracted many researchers' attention¹⁷⁻²². For example, two task functional MRI (fMRI)
11 studies focusing on male sexual arousal reported that compared with healthy controls,
12 patients with pED manifested lower penile tumescence, larger activities in left superior
13 parietal lobe, ventromedial prefrontal cortex and posterior cingulate cortex, as well as
14 altered intrinsic functional connectivity at default mode network and salience network
15 during visual erotic stimuli^{23 24}. Resting-state fMRI studies also suggested that patients
16 with pED not only displayed aberrant spontaneous activities at the right anterior insula,
17 but also showed abnormal connection patterns between right anterior insula and right
18 dorsolateral prefrontal cortex as well as right anterior insula and right temporoparietal;
19 furthermore, both the aberrant activities at right anterior insula and the abnormal
20 functional connection between right anterior insula and right temporoparietal were
21 positively correlated with the scores of International Index of Erectile Function (IIEF)
22 scale in participants^{25 26}. With structural MRI, researchers found that compared with
23 healthy controls, pED sufferers presented grey matter atrophy in some subcortical
24 structures including amygdala and nucleus accumbens, and the atrophied degree of left
25 nucleus accumbens showed a close correlation with patients' decreased erectile
26 function²⁷. Moreover, our previous study²⁸ also detected that patients with pED had
27 significant microstructure alterations at splenium of the corpus callosum and multiple
28 white matter regions.

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

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2
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4 1 a genitourinary disease, but also had abnormal alterations in both brain structure and
5
6 2 function. However, there is still no integrated study to summarize the scattered evidence
7
8 3 in individual studies, and the central pathological alterations associated with pED
9
10 4 remain unclear. Therefore, launching a rigorous systematic review to synthesize the
11
12 5 hitherto existing studies is necessary, which will improve our knowledge to the
13
14 6 neurological underpinnings of pED and help to better understand the role of CNS in
15
16 7 sexual activity.

8 **Objectives**

9 The objective of this systematic review is to integrate and assess the evidence of the
10
11 10 impact of pED on men's brain and to contribute a comprehensive summary of brain
12
13 11 structural and functional alterations in patients with pED. Furthermore, this review also
14
15 12 aims to synthesize the probable associations between the statistical differences
16
17 13 observed in some brain regions regarding the function or structure and the clinical
18
19 14 characters such as behavioural /psychophysiological data, disease-related scales, QoL
20
21 15 scales, and emotional scales in patients with pED.

16 **METHODS**

17 This protocol follows the Preferred Reporting Items for Systematic Reviews and
18
19 18 Meta-Analysis Protocols (PRISMA-P) 2015 statement²⁹ and has been registered at the
20
21 19 PROSPERO International Prospective Register of Systematic Reviews of the
22
23 20 University of York (registration number: CRD42019117206).

21 **Eligibility criteria**

22 The inclusion and exclusion criteria of studies will be described with the following
23
24 23 items:

24 ***Types of study***

25 The case-control studies, cohort studies, as well as randomized controlled trials will be
26
27 26 included only if the original data of neuroimaging findings could be extracted. The case
28
29 27 reports, narrative or systematic reviews, meta-analyses, letters, and other second-hand
30
31 28 studies will be excluded.

1 **Study design**

2 Neuroimaging studies which centred on the differences of brain structure, brain
3 functional activity, structural and functional connectivity, etc. between patients with
4 pED and healthy controls will be included. The longitudinal studies focusing on the
5 management of pED will also be considered as long as the baseline neuroimaging data
6 were reported. Both the resting-state and task neuroimaging studies will be included,
7 and no neuroimaging modality will be restricted. Any publication acquired data using
8 multimodal neuroimaging techniques from the same participants will be collected
9 separately in this review³⁰.

10 **Participants**

11 Participants will be limited at the clearly diagnosed patients with pED and the parallel
12 healthy controls. The minimum sample size for inclusion is restricted at 12 participants
13 per group according to previous studies³⁰⁻³². The race, age, and disease conditions
14 (drug-naïve or drug-invented) of participants will not be restricted in this review.

15 **Exposure**

16 Patients with pED should be diagnosed with comprehensive history taking, physical
17 examinations and even specific examinations according to the diagnostic guidelines
18 of European Association of Urology (EAU)³³⁻³⁵, American Urological Association
19 (AUA)^{36 37} or other authoritative organizations³⁸. The organic ED or mixed ED, or
20 patients with other andrological or cardiovascular complications will be excluded.
21 Some studies enrolling patients without clear discrimination of subtypes of ED will be
22 considered after the comprehensive full-text assessment or contacting the authors to
23 identify the patients as pED.

24 **Comparators**

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

1 ***Outcome measures***

2 The primary outcomes of the included studies should be the functional and structural
3 alterations in the brain of the patients with pED. The outcomes of brain structure include
4 white matter microstructure, gray matter density and volume, and structural
5 connectivity. The outcomes of brain function include whole-brain /region-of-interest
6 functional activity, functional connectivity (fMRI based on blood-oxygen-level-
7 dependent (BOLD) signal or cerebral blood flow), brain molecular metabolism
8 (Positron Emission Tomography (PET), Single-Photon Emission Computed
9 Tomography (SPECT)), neurochemical activity (Magnetic Resonance Spectroscopy
10 (MRS)) as well as brain electrical activity (Electroencephalogram (EEG)), etc. The
11 secondary outcomes of these studies may contain behavioural /psychophysiological
12 data (such as genital responses, heart and respiratory rates^{23 24}), symptom-related
13 scales (such as IIEF-5³⁹, Quality of Erection Questionnaire (QEQ)⁴⁰, and the Erection
14 Hardness Score (EHS))⁴¹, QoL questionnaire (the Sexual Life Quality Questionnaire
15 (SLQQ))⁴² and psychological assessment scales (such as Self-Rating Anxiety Scale
16 (SAS)⁴³, Self-Rating Depression Scale (SDS)⁴⁴, and Brief Psychiatric Rating Scale
17 (BPRS)⁴⁵). Studies only have primary outcome will also be included in this review.

18 ***Report characteristics***

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

23 ***Searching strategy***

24 Electronic searching will be conducted in PubMed, EMBASE, Web of Science, China
25 Biology Medicine Database (CBM) and China National Knowledge Infrastructure
26 (CNKI) using the medical subject headings (MeSH) terms. The searching strategies of
27 PubMed (English) and CNKI (Chinese) are displayed in Table 1 and will be replicated
28 for other electronic databases. Thereafter, the snowballing searching strategy will be

1 employed to find other eligible studies according to the reference lists of enrolled
2 literature. In addition, the WHO International Clinical Trials Registry Platform will also
3 be searched to mining more potential results.

4 [Insert Table 1 here]

5 **Selection process**

6 Covidence (<https://www.covidence.org>), the Cochrane Library recommend online
7 systematic review management system, will be used to manage literature. The initial
8 searching results with the above strategies will be uploaded to Covidence. After
9 duplicates removed, TY will screen the title and abstract to remove the obviously
10 irrelevant records; and then, the two reviewers (TY and JX) will parallelly complete the
11 abstract and full-text review. Any disagreement between TY and JX will be
12 reconsidered by a third reviewer (ZL). In order to assess the reliability of the selection
13 criteria and the inter-rater agreement between the two reviewers, the Cohen's Kappa
14 will be calculated at the parallel selection stage, and the Kappa coefficient (k) over 0.75
15 indicates high reliability⁴⁶. The selection process of records will be reported using the
16 PRISMA flow diagram⁴⁷ and the eliminated reasons for those ineligible records will be
17 detailed reported.

18 **Data collection**

19 The two independent reviewers (TY and JX) will doubly extract data using a standard
20 data extraction spreadsheet in Excel. Again, any inconsistency between these two
21 reviewers will also be consulted and judged by ZL, the third reviewer.

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

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

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

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

8 **Outcomes and prioritization**

9 The primary outcome of this review is the significant altered cerebral regions in patients
10 with pED compared with healthy controls. Due to the variety of analytical methods and
11 great heterogeneity of the statistical thresholds of studies (e.g. voxel cluster size
12 thresholds, statistic magnitudes, methods of correcting for multiple comparisons), it is
13 unrealistic to set a uniform significance threshold. Therefore, the ‘significant’ results
14 will follow the study authors’ own criteria⁴⁸. Some neuroimaging studies also reported
15 results trending to significant or significant only before correction⁴⁸. For a more
16 comprehensive view, these regions will be collected with special symbols in the
17 qualitative synthesis. The secondary outcome of this review is the associations of the
18 altered cerebral structure /function and the clinical characters which mainly include
19 behavioural /psychophysiological data, disease-related scales, QoL scales, emotional
20 scales, and so on. The values of these clinical characters will be recorded, and they
21 might be used to explain the inter-studies variability when necessary.

22 **Quality assessment**

23 There are no standardized criteria for quality assessment of neuroimaging studies^{49 50}.
24 Authors of the previous systematic reviews always developed their own quality
25 assessment tools based on some existing tools (such as QUADAS-2, Newcastle-Ottawa
26 Scale (NOS))^{49 51-55}. However, because of the diverse objects of studies, the currently
27 existing assessment tools are not very suitable for our review. Therefore, after referring
28 the NOS⁵⁶, some published systematic reviews^{49-51 57} and the Committee on Best

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4 1 Practices in Data Analysis and Sharing in Neuroimaging Using MRI⁵⁸
5 (http://www.humanbrainmapping.org), a customized checklist is proposed in the
6
7 2
8 3 current review. This checklist will be used to evaluate the quality of the included studies
9
10 4 from 9 items (Table 2). Each item is scored as 1 (Yes) or 0 (No or Don't know), and
11
12 5 the summation of items generates an overall quality score (0–9 points). The quality
13
14 6 levels of studies are defined as high (8–9 points), medium (5–7points) and low (0–4
15
16 7 points).

17
18 8 [Insert Table 2 here]

19 9 Quality assessment will be performed by a professional assessor (LL) who is
20
21 10 experienced with quality assessment scoring and a non-professional assessor (RS) who
22
23 11 have never engaged in quality assessment of systematic reviews. These two assessors
24
25 12 will independently evaluate the enrolled studies based on the checklist; any discrepancy
26
27 13 will also be reconsidered by the third reviewer (ZL). Again, the inter-rater agreement
28
29 14 will be assessed by Cohen's Kappa with the threshold $k > 0.75$ indicating high reliability.

31 **Data Synthesis**

32
33 16 Firstly, collected data including publication information, methodologies, and the
34
35 17 significant findings of studies will be summarized with a table. And then, a qualitative
36
37 18 review will be performed to synthesize the brain structural and functional alterations
38
39 19 and the correlations between these altered cerebral structure/ function and the clinical
40
41 20 characters in patients with pED. For a clearer presentation, these findings will be
42
43 21 integrated separately according to the task /resting design and neuroimaging modalities.
44
45 22 If feasible (17 or more resting-state studies are included⁵⁹), an activity likelihood
46
47 23 estimation meta-analysis^{60 61} will be launched to quantitatively synthesize the
48
49 24 differences of cerebral structure and function between patients with pED and healthy
50
51 25 controls. The subgroup analyses will not be performed in this review. The strength of
52
53 26 evidence for the final conclusion of this review will be determined by the checklist
54
55 27 described above.

57 **CONCLUSION**

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4 1 While neuroimaging studies have verified the existence of brain structural and
5 2 functional alterations in patients with pED, the scattered neuroimaging biomarkers of
6 3 pED in individual studies have yet been summarized. Therefore, this systematic review
7 4 is launched, aiming to synthesize the central pathological characters and the
8 5 associations between the altered brain structure /function and clinical characters of pED.
9 6 The current review will be the first to synthesize the neuroimaging evidence of pED in
10 7 a systematic way, to include a meta-analysis of the findings, and the first to assess the
11 8 quality of these neuroimaging studies. This work will provide a coherent synthesis of
12 9 the recent neuroimaging studies on pED and improve our knowledge to the neurological
13 10 underpinnings of pED.

11 **Patient and public involvement**

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

13 **Ethics and dissemination**

14 Ethical approval is not required for this study. This review will be published in a peer-
15 15 reviewed journal and presented at conferences.

16 **Contributors**

17 Peihai Zhang was responsible for this study. Tao Yin, Zhengjie Li and Peihai Zhang
18 18 conceived and designed the study. Tao Yin, Zhengjie Li and Jing Xiong participated in
19 19 drafting the protocol and preparing the manuscript. Lei Lan, Ruirui Sun and Feiqiang
20 20 Ren provided feedback on the study design and protocol. All authors read and approved
21 21 the final manuscript.

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25 **Competing interests**

26 The authors declare that they have no competing interests.

27 **Patient consent**

1 Not required.

2 **Data sharing statement**

3 This paper does not include the original data.

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1 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	#9 MRI [主题词]
OR #8	#10 PET [主题词]
#10 Neuroimaging [MeSH Terms]	#11 SPECT [主题词]
#11 Functional Neuroimaging [MeSH Terms]	#12 EEG [主题词]
#12 Brain imaging [All Fields]	#13 MRS [主题词]
#13 Magnetic resonance imaging [MeSH Terms]	#14 DTI [主题词]
#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 #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	

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1 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, handedness, 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.			

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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.**

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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Primary Subject Heading:	Sexual health
Secondary Subject Heading:	Urology
Keywords:	Neuroimaging, Magnetic resonance imaging < RADIOLOGY & IMAGING, Psychogenic erectile dysfunction, Activation likelihood estimation

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5 **1 Title page**
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8 **2 Title**
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10 Neuroimaging biomarkers of psychogenic erectile dysfunction: protocol for a
11 systematic review
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1 **Neuroimaging biomarkers of psychogenic erectile dysfunction:** 2 **protocol for a systematic review**

3 **ABSTRACT**

4 **Introduction**

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

13 **Methods and analysis**

14 Five databases (PubMed, EMBASE, Web of Science, China Biology Medicine
15 Database, and China National Knowledge Infrastructure) will be systematically
16 searched from inception to 1 October 2019 (the anticipated completion date of this
17 review), with language restricted to English and Chinese. Studies focusing on the
18 structural or functional alterations in patients with pED will be retrieved. The study
19 selection process will follow the PRISMA guideline and quality assessment will be
20 conducted with a customized checklist. After data extraction, a qualitative review will
21 be performed to synthesize the structural and functional brain alterations as well as the
22 correlations between the altered cerebral structures and functions and the clinical
23 characteristics of patients with pED. If the collected data make it feasible, an activation
24 likelihood estimation meta-analysis will also be launched.

25 **Ethics and dissemination**

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

28 **PROSPERO registration number**

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4 1 CRD42019117206

5
6 2 **Keywords**

7 3 Psychogenic erectile dysfunction, Neuroimaging, Magnetic resonance imaging,
8 4 Activation likelihood estimation

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11 5 **Strengths and limitations of this study**

12 6 1. This is the first systematic review and meta-analysis that integrates and assesses the
13 7 central pathological characteristics of pED.

14 8 2. Qualitative and quantitative synthesis (activation likelihood estimation meta-analysis)
15 9 will both be used in this study.

16 10 3. A customized checklist is proposed to evaluate the quality of the included studies
17 11 according to the purpose of this review.

18 12 4. This review does not restrict the race, age, disease conditions of participants or pre-
19 13 processing procedures of included studies, which will increase the heterogeneity of
20 14 included studies and may increase the risk of bias of the review.

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33 16 **INTRODUCTION**

34 17 Erectile dysfunction (ED) is the most common male sexual disorder. It is characterized
35 18 by the persistent inability to attain or maintain an adequate erection to obtain
36 19 satisfactory sexual intercourse regardless of the capability of ejaculation.¹⁻³ According
37 20 to epidemiological studies, approximately 37% of men over 70 years old and 11% of
38 21 men over 30 years old suffer from this sexual dysfunction.⁴ As a physical and
39 22 psychosocial illness, ED not only impairs male sexual confidence and satisfaction but
40 23 also severely impacts the quality of life (QoL)^{5 6} and relationships⁷ of patients and their
41 24 partners. More importantly, ED has been increasingly regarded as an independent risk
42 25 factor for cardiovascular diseases.^{8 9} According to its different causes^{10 11}, ED is
43 26 subdivided into psychogenic ED (pED), organic ED, and mixed ED. Different from
44 27 organic ED, which has clear causes and pathological characteristics, pED is generally
45 28 caused by uncertain psychological factors^{12 13} and lacks specific biomarkers.

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58 29 **Rationale for review**

1 Penile erection is a complex physiological process modulated by the central nervous
2 system and mediated by several neurotransmitters and neuropeptides.^{14 15} A meta-
3 analysis identified that penile erection was regulated by several cerebral regions; the
4 activities of the insular cortex, claustrum, putamen, and anterior midcingulate cortex
5 were consistently positively correlated with male penile erection.¹⁶ With the close
6 relationship between the brain and penile erection being widely accepted, using
7 neuroimaging techniques to explore the central pathological characteristics of pED has
8 attracted the attention of many researchers.¹⁷⁻²² In the process, some well-designed
9 cognitive-behavioural models have been developed to further explain the
10 neurobiological underpinning of abnormal behaviour in patients with ED.^{23 24} For
11 example, two task functional magnetic resonance imaging (fMRI) studies focusing on
12 male sexual arousal reported that, when compared with healthy controls, patients with
13 pED manifested lower penile tumescence, more activity in the left superior parietal lobe,
14 ventromedial prefrontal cortex, and posterior cingulate cortex, and altered intrinsic
15 functional connectivity of the default mode network and salience network during visual
16 erotic stimuli.^{23 24} Resting-state fMRI studies also suggested that patients with pED not
17 only displayed aberrant spontaneous activities at the right anterior insula but also
18 showed abnormal connection patterns between the right anterior insula and right
19 dorsolateral prefrontal cortex as well as between the right anterior insula and right
20 temporoparietal cortex. Furthermore, both the aberrant activities of the right anterior
21 insula and the abnormal functional connection between the right anterior insula and
22 right temporoparietal cortex were positively correlated with participant scores on the
23 International Index of Erectile Function (IIEF) .^{25 26} On structural MRI, researchers
24 found that, when compared with healthy controls, pED sufferers presented grey matter
25 atrophy in some subcortical structures, including the amygdala and nucleus accumbens,
26 and the atrophied degree of left nucleus accumbens showed a close correlation with
27 decreased erectile function.²⁷ Moreover, our previous study detected that patients with
28 pED had significant microstructure alterations at the splenium of the corpus callosum
29 and in multiple white matter regions.²⁸

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4 1 Based on these neuroimaging studies, we may easily conclude that pED is not only a
5 2 genitourinary disease but also is associated with abnormal alterations in both brain
6 3 structure and brain function. However, there is no integrated study summarizing the
7 4 scattered evidence of individual studies, and the central pathological alterations
8 5 associated with pED remain unclear. Therefore, launching a rigorous systematic review
9 6 to synthesize the hitherto existing studies is necessary to improve knowledge of the
10 7 neurological underpinnings of pED and increase understanding of the role of the central
11 8 nervous system in sexual activity.

9 **Objectives**

10 The objective of this systematic review is to integrate and assess the evidence of the
11 impact of pED on the brain and to contribute a comprehensive summary of structural
12 and functional brain alterations in patients with pED. This review also aims to
13 synthesize correlations between the differences observed in some brain regions related
14 to function or structure and the clinical characteristics of patients with pED, such as
15 behavioural and psychophysiological data and data obtained from disease-related scales,
16 QoL scales, and emotional scales.

17 **METHODS**

18 This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-
19 Analysis Protocols (PRISMA-P) 2015 statement²⁹ and has been registered at the
20 PROSPERO International Prospective Register of Systematic Reviews of the
21 University of York (registration number CRD42019117206).

22 **Eligibility criteria**

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

24 **Study types**

25 Case control studies, cohort studies, and randomized controlled trials will be included
26 only if the original neuroimaging data can be extracted. Case reports, narrative or
27 systematic reviews, meta-analyses, letters, and other second-hand studies will be
28 excluded.

29 **Study design**

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4 1 Neuroimaging studies centred on the differences between the brain structure, brain
5
6 2 functional activity, and structural and functional connectivity of patients with pED and
7
8 3 those of healthy controls will be included. Longitudinal studies focusing on the
9
10 4 management of pED will be considered as long as the baseline neuroimaging data are
11
12 5 reported. Both resting-state and task neuroimaging studies will be included, and no
13
14 6 neuroimaging modality will be precluded. Any publication acquired data using
15
16 7 multimodal neuroimaging techniques from the same participants will be collected
17
18 8 separately in this review.³⁰

9 Participants

10 Studies containing both patients with pED and parallel healthy controls will be
11
12 11 considered for inclusion. The minimum sample size for inclusion will be restricted to
13
14 12 12 participants per group, according to previous studies.³⁰⁻³² The race, age, and disease
15
16 13 conditions (drug-naïve or drug-invented) of participants will not be restricted in this
17
18 14 review.

15 Exposure

16 Patients with pED should be diagnosed by comprehensive history taking, physical
17
18 16 examination, and even specific examinations according to the diagnostic guidelines of
19
20 17 the European Association of Urology (EAU)³³⁻³⁵, the American Urological Association
21
22 18 (AUA)^{36 37}, or other authoritative organizations³⁸. Patients with organic ED or mixed
23
24 19 ED or with other andrological or cardiovascular complications will be excluded. Some
25
26 20 studies enrolling patients without clear discrimination of subtypes of ED will be
27
28 21 considered after comprehensive full-text assessment or contact with the authors to
29
30 22 identify the participants as patients with pED.

23 Comparators

24 Participation of a parallel healthy control group in the study is required for inclusion in
25
26 25 the current review. Healthy controls must have no prior diagnosis of ED at enrolment,
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28 26 and this must be verified by clinical examination during the study. Studies absenting
29
30 27 from healthy controls will be excluded.

29 Outcome measures

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4 1 The primary outcomes of the included studies should be functional and structural brain
5
6 2 alterations of the patients with pED. Brain structure outcomes are related to white
7
8 3 matter microstructure, grey matter density or volume, or structural connectivity.
9
10 4 Outcomes related to brain function include whole-brain or region-of-interest functional
11
12 5 activity or functional connectivity (fMRI based on blood-oxygen-level-dependent
13
14 6 signal or cerebral blood flow), brain molecular metabolism (positron emission
15
16 7 tomography or single-photon emission computed tomography); neurochemical activity
17
18 8 (magnetic resonance spectroscopy); or brain electrical activity (electroencephalogram).
19
20 9 The secondary outcomes of these studies may contain behavioural and
21
22 10 psychophysiological data (such as genital responses and heart and respiratory rates²³
23
24 11 ²⁴); symptom-related scales (such as IIEF-5³⁹, Quality of Erection Questionnaire
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26 12 (QEQ)⁴⁰, and the Erection Hardness Score (EHS))⁴¹; QoL questionnaire (the Sexual
27
28 13 Life Quality Questionnaire (SLQQ))⁴²; or psychological assessment scales (such as the
29
30 14 Self-Rating Anxiety Scale (SAS)⁴³, the Self-Rating Depression Scale (SDS)⁴⁴, and the
31
32 15 Brief Psychiatric Rating Scale (BPRS)⁴⁵). Studies with only a primary outcome will
33
34 16 also be included in this review.

17 Report characteristics

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

22 **Searching strategy**

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

1 searched for potential results.

2 [Insert Table 1 here]

3 **Selection process**

4 Covidence (<https://www.covidence.org>), the Cochrane Library-recommended online
5 systematic review management system, will be used to manage literature. The initial
6 searching results obtained following the above strategies will be uploaded to Covidence.
7 After duplicates are removed, TY will screen the title and abstract to remove the
8 obviously irrelevant records. Then two reviewers (TY and JX) will complete the
9 abstract and full-text review in parallel. Any disagreement between TY and JX will be
10 reconsidered by a third reviewer (ZL). In order to assess the reliability of the selection
11 criteria and inter-rater agreement between the two reviewers, Cohen's kappa will be
12 calculated at the parallel selection stage; a kappa coefficient (k) over 0.75 will indicate
13 high reliability.⁴⁶ The record selection process will be reported using the PRISMA flow
14 diagram⁴⁷ and elimination reasons for ineligible records will be reported in detail.

15 **Data collection**

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

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

- 20 ● Publication information: title, first author, publishing time, country or region,
21 and funding support.
- 22 ● Details of methodology: participants, sample size, diagnostic criteria,
23 demographic characteristics (including age, handedness, ethnicity, and
24 education), imaging modalities, data analysis strategies, pED-related
25 cognitive-behavioural models, and clinical outcomes.
- 26 ● Results: the significant altered cerebral regions (described by peak MNI
27 /Talairach coordinate, cluster size, and statistical threshold); the value of
28 clinical characteristics (behavioural and psychophysiological data, disease-
29 related scales, QoL scales, emotional scales, etc.); and the correlations between

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4 1 imaging data and clinical data.

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6 2 Any missing information or questions about the above data will be settled by contacting
7
8 3 the authors. If no clarification is provided after 4 weeks, the study will be included in
9
10 4 the final analysis with the missing information marked.

11 5 **Outcomes and prioritization**

12
13 6 The primary outcome of this review will be the significantly altered cerebral regions in
14
15 7 patients with pED when compared with healthy controls. Due to the variety of
16
17 8 analytical methods and great heterogeneity of the studies' statistical thresholds (e.g.,
18
19 9 voxel cluster size thresholds, statistical magnitudes, methods of correcting for multiple
20
21 10 comparisons), it is unrealistic to set a uniform significance threshold. Therefore, the
22
23 11 significance of results will be determined by the study authors' own criteria.⁴⁸ Some
24
25 12 neuroimaging studies also report results trending to significant or significant only
26
27 13 before correction.⁴⁸ For a more comprehensive view, these regions will be collected
28
29 14 with special symbols in the qualitative synthesis. The secondary outcome of this review
30
31 15 will be the associations between the altered cerebral structure and function and the
32
33 16 clinical characteristics, which mainly include behavioural and psychophysiological
34
35 17 data, disease-related scales, QoL scales, emotional scales, and so on. The values of
36
37 18 these clinical characteristics will be recorded and may be used to explain interstudy
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39 19 variability when necessary.

40 20 **Quality assessment**

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42 21 There are no standardized criteria for quality assessment of neuroimaging studies.⁴⁹⁻⁵⁰
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44 22 Authors of previous systematic reviews have always developed their own quality
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46 23 assessment tools based on existing tools (such as QUADAS-2 and the Newcastle-
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48 24 Ottawa Scale (NOS)).⁴⁹⁻⁵¹⁻⁵⁵ However, because of the diverse study objectives, current
49
50 25 assessment tools are not suitable for this review. Therefore, after referring to the NOS⁵⁶,
51
52 26 some published systematic reviews,⁴⁹⁻⁵¹⁻⁵⁷ and the Committee on Best Practices in Data
53
54 27 Analysis and Sharing in Neuroimaging Using MRI⁵⁸
55
56 28 (<http://www.humanbrainmapping.org>), a customized checklist is proposed for the
57
58 29 current review. This checklist will be used to evaluate the quality of the included studies
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1 based on 9 items (Table 2). Each item is scored as 1 (Yes) or 0 (No or Don't know),
2 and the summation of items generates an overall quality score (0–9 points). Each study's
3 quality is defined as high (8–9 points), medium (5–7points), or low (0–4 points).

4 [Insert Table 2 here]

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

11 **Data Synthesis**

12 The collected data, including publication information, methodologies, and significant
13 study findings, will be summarized in a table. Methodologies and neuroimaging results
14 will then be pooled and described in detail. The total and average sample size, age range
15 of participants, and mean duration of patients of included studies will be calculated, and
16 the cognitive-behavioural models, outcomes of behavioural and psychophysiological
17 measurement, disease-related scales, QoL scales, and emotional scales will be
18 summarized. A qualitative review will be performed to synthesize the structural and
19 functional brain alterations and correlations between these alterations and the clinical
20 characteristics of patients with pED. For more clear presentation, these findings will be
21 integrated separately according to task or resting design and neuroimaging modality. If
22 feasible (if 17 or more resting-state studies are included⁵⁹), an activation likelihood
23 estimation meta-analysis^{60 61} will be launched to quantitatively synthesize the
24 differences in cerebral structure and function between patients with pED and healthy
25 controls. Subgroup analyses will not be performed in this review. The strength of
26 evidence of this review will be determined by the checklist described above.

27 **CONCLUSION**

28 Although neuroimaging studies have verified the existence of structural and functional
29 brain alterations in patients with pED, the scattered neuroimaging biomarkers of pED

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4 1 in individual studies have not yet been summarized. Therefore, this systematic review
5 2 is launched, aiming to synthesize the central pathological characteristics and the
6 3 associations between the altered cerebral structure and function and the clinical
7 4 characteristics of pED. The current review will be the first to synthesize the
8 5 neuroimaging evidence of pED in a systematic way, to include a meta-analysis of the
9 6 findings, and to assess the quality of these neuroimaging studies. This work will provide
10 7 a coherent synthesis of the recent neuroimaging studies on pED and improve
11 8 knowledge of the neurological underpinnings of pED.

9 **Patient and public involvement**

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

11 **Ethics and dissemination**

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

14 **Contributors**

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

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21 This work is financially supported by the National Natural Science Foundation of China
22 (NO.81774137).

23 **Competing interests**

24 The authors declare that they have no competing interests.

25 **Patient consent**

26 Not required.

27 **Data sharing statement**

28 This paper does not include the original data.

29 **Reference**

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1 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	#9 MRI [主题词]
OR #8	#10 PET [主题词]
#10 Neuroimaging [MeSH Terms]	#11 SPECT [主题词]
#11 Functional Neuroimaging [MeSH Terms]	#12 EEG [主题词]
#12 Brain imaging [All Fields]	#13 MRS [主题词]
#13 Magnetic resonance imaging [MeSH Terms]	#14 DTI [主题词]
#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 #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	

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1 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, handedness, 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.			

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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

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		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

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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.**

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.