

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Neuroimaging biomarkers of psychogenic erectile dysfunction: protocol for a systematic review
AUTHORS	Yin, Tao; Li, Zhengjie; Xiong, Jing; Lan, L.; SUN, RUIRUI; Ren, Feiqiang; Zhang, Peihai

VERSION 1 – REVIEW

REVIEWER	Moustafa El Taieb Aswan University Egypt
REVIEW RETURNED	15-Mar-2019

GENERAL COMMENTS	I have the pleasure to revise this protocol. The protocol is well written and organized. I have some concerns: will the protocol be published in this stage and in its form? What is the value of publication of a protocol of study that not yet done? Does the scope of the journal include publishing protocols of future papers
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REVIEWER	Hong Yin Xijing Hospital
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	<p>This manuscript focused on the verification of the existence of structural and functional alteration in the brain of pED patients. While the presentation in this manuscript is intact and logical, some concerns should be addressed.</p> <p>1. Abstract: Grammar errors: "Previous studies had found that psychogenic ED (pED), the main subtype of ED, was more than a 8 genitourinary disease, it also had abnormal alterations in both brain structure and 9 function." Key words should include psychogenic ED instead of ED.</p> <p>2. Limitation: No expression about the limitation of established protocols for imaging studies and image pre-processing procedures, such as smoothing, modalities, registration, data analysis.</p> <p>There is lack of evidence about the studies included in the paper about the characteristics of pED (chronic or acute) is consistent and whether the pED is treated or not?</p>
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	<p>3. Introduction Clear definition of ED is still lacking. “Moreover, our previous studies²⁴ also determined that pED patients have significant white matter microstructure alterations.” Only one study is referred. Grammar error “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 function” Grammar error: ” 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.”</p> <p>4. Objective What is included as the clinical variables?</p> <p>5. Methods (1) The studies included should contain information on the sample sizes, disease conditions and the thresholds for each study should be expressed. (2) How are the differences between different guidelines, such as EAU, AUA, etc.? (3) Diagnostic criteria of pED should be included in this section. (4) The studies included might be “functional or structural studies” as I assumed, instead of “functional and structural study” (5) grammar error “Some neuroimaging studies also reported results trending to significance or significant results only before correction, for a more comprehensive view, these regions will be collected with 25 special symbols in qualitative synthesis.” (6) Will studies without secondary outcome include in the study?</p> <p>6. References: Some references included DOI and some did not.</p>
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REVIEWER	Nicoletta Cera University of Porto, Portugal
REVIEW RETURNED	21-May-2019

GENERAL COMMENTS	<p>1. the authors define the various sub types of ED. It should be better to subdivide in 2 big macro-categories: psychogenic and organic.</p> <p>2. the authors mention some of the principal findings about neuroimaging studies. They omitted completely the principal cognitive -behavioral models developed to explain the ED. So, it is not clear the link between non-imaging studies and imaging studies. Moreover, only few imaging results have been mentioned.</p> <p>3. what did the authors mean with neurobehavioral stimuli? In sex research there a lot of experimental designs. Please explain.</p> <p>4. Objectives: “Furthermore, this review also aims to synthesize the probable correlations between these altered cerebral regions and the clinical variables.” Please reformulate this sentence. Maybe it 'd more correct to write about the statistical differences observed in some brain regions regarding the bold signal (fMRI) or in the volume.</p> <p>5. In the text the authors did not mention the eventual metanalyses performed on behavioral /psychometric /hormonal data included in the imaging studies. Maybe it is important to explain the inter-studies variability.</p> <p>6. Several functional imaging studies collected also the genital responses. Some studies collected also heart and respiratory</p>
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	<p>rates. These psychophysiological data are important, overall, in the distinction between general arousal and sexual arousal and are important for pED.</p> <p>7. According to me it is difficult to compare results from “task-fMRI”(for example) and rs-fMRI studies. Please explain In which way different results (form rs or ICA, tasks and graph theory) could be compared.</p> <p>8. “Again, the inter-rater reliability will be assessed by kappa value.”- Please, specify the statistical test (Cohen and the range values).</p> <p>9. Conclusion. The conclusion section is very limited.</p>
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REVIEWER	Nele Brusselaers, Associate Professor Karolinska Institutet, Stockholm, Sweden
REVIEW RETURNED	14-Jun-2019

GENERAL COMMENTS	<p>I read with interest the study protocol for a systematic review on erectile dysfunction and brain alterations. Looking at the study question and short description of the field, I guess conducting a meta-analysis based on the retrieved studies will be challenging, especially since the outcome is not (cannot) be clearly defined.</p> <ul style="list-style-type: none"> - The search methodology seems sound, although I would not put an end date on it (thinking that time flies and it could be useful to do an update close to submission) - Study outcome: I don't think it is an optimal definition for the outcome, since you already claim that you will only look at “significant” altered cerebral regions. So you suppose there is a change, and you imply that you will not include studies not reporting changes. The statistical methods could be described in more detail, i.e how do the data look like and how will they be pooled? - Some revisions of the language are required - I would suggest to use the term men instead of males. Although correct English, men is more respectful towards study participants + it is a problem for adults. - What do you mean with professional assessor? Do you mean someone experienced with quality assessment scoring, or a professional working with individuals with ED? - I am not a fan of using kappa statistics to grade correlation between reviewers, since one of both individuals will anyway be more careful in excluding articles than the other. Most important is that all eligible articles are identified. It could therefore be considered that the first stage(s) of screening are done by 1 researcher to remove all clearly irrelevant articles, and that from abstract or fulltext level, the screening is done in parallel. But again, most important is that all relevant articles are maintained. - Some language editing is needed.
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VERSION 1 – AUTHOR RESPONSE

Response to Reviewer: 1

Comments:

1. will the protocol be published in this stage and in its form?
2. What is the value of publication of a protocol of study that not yet done?
3. Does the scope of the journal include publishing protocols of future papers

Answers:

1. The Cochrane Database of Systematic Reviews (Cochrane Library) suggests authors to publish their comprehensive protocol for a review prior to knowledge of the available studies to reduce the impact of review authors' biases and promote transparency of methods and processes (see <http://handbook-5-1.cochrane.org/> Cochrane Handbook for Systematic Reviews /Part 1 / 2.1 Rationale for protocols). So, we think it is necessary to publish this protocol in this stage.

2. Publishing protocol is a feasible approach to help prevent unnecessary duplication of work. A comprehensive protocol makes available more information than is currently required by trial registries and increases transparency of methods and processes. Furthermore, we hope to improve the quality of this systematic review through the peer review process of the protocol.

3. According to the submission guidelines, BMJ open will consider to publish protocols of systematic reviews.

Response to Reviewer: 2

Comments & Answers:

1. Abstract:

Grammar errors: "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."

The grammar errors had been corrected. [Line 6-8, Page 2]

Key words should include psychogenic ED instead of ED.

The key words had been changed. [Line 4, Page 3]

2. Limitation:

No expression about the limitation of established protocols for imaging studies and image pre-processing procedures, such as smoothing, modalities, registration, data analysis.

There is lack of evidence about the studies included in the paper about the characteristics of pED (chronic or acute) is consistent and whether the pED is treated or not?

The limitation about the disease condition of patients and processing procedures of included studies had been declared in the Strengths and limitations of this study section. [Line 13-15, Page 3]

3. Introduction

Clear definition of ED is still lacking.

The definition of ED had been complemented according to the references from JAMA and BMJ. [Line 17-19, Page 3]

"Moreover, our previous studies²⁴ also determined that pED patients have significant white matter microstructure alterations." Only one study is referred.

'previous studies' had been changed to 'previous study'. [Line 25, Page 4]

Grammar error "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 function"

The grammar errors had been corrected. [Line 28-29, Page 4]

Grammar error: " 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."

The grammar errors had been corrected. [Line 3-6, Page 5]

4. Objective

What is included as the clinical variables?

The main components of clinical variables had been complemented. [Line 12-14, Page 5]

5. Methods

(1) The studies included should contain information on the sample sizes, disease conditions and the thresholds for each study should be expressed.

The restriction of sample sizes and disease conditions were expressed at Participants section [Line 11-13, Page 6], and the restriction of thresholds for each study were expressed at Outcomes and prioritization section [Line 7-11, Page 9]. pED is a chronic disorder which must be diagnosed with a course more than 6 months. So, the disease conditions (chronic or acute) was not described in the Methods section.

(2) How are the differences between different guidelines, such as EAU, AUA, etc.?

There are a bit differences among different diagnosing guidelines, such as specific physical examinations and laboratory tests. However, the overall diagnostic principle of different guidelines is similar. We give examples of kinds of guidelines aiming to illustrate that only studies with definitely diagnosed patients would be included in this review.

(3) Diagnostic criteria of pED should be included in this section.

The diagnostic criteria for patients of studies were an important information and we described this item in the Exposure section [Line 15-22, Page 6]. Generally speaking, for a systematic review which did not enroll individual patients, a specially established section for diagnostic criterion is not indispensable.

(4) The studies included might be “functional or structural studies” as I assumed, instead of “functional and structural study”

The expression of ‘functional and structural study’ had been revised in the manuscript.

(5) grammar error “Some neuroimaging studies also reported results trending to significance or significant results only before correction, for a more comprehensive view, these regions will be collected with 25 special symbols in qualitative synthesis.”

The grammar errors had been corrected. [Line 11-14, Page 9]

(6) Will studies without secondary outcome include in the study?

Studies without secondary outcome will also be included in the review. [Line16, Page 7]

6. References:

Some references included DOI and some did not.

The references had been checked and the all the DOI had been updated.

Response to Reviewer: 3

Comments & Answers:

1. the authors define the various sub types of ED. It should be better to subdivide in 2 big macro-categories: psychogenic and organic.

The types of ED had been subdivided into psychogenic, organic and mixed in the manuscript. [Line 25-26, Page 3]

2. the authors mention some of the principal findings about neuroimaging studies. They omitted completely the principal cognitive -behavioral models developed to explain the ED. So, it is not clear the link between non-imaging studies and imaging studies. Moreover, only few imaging results have been mentioned.

The associations of cognitive –behavioral results and the imaging results had been complemented in the Introduction section, and the examples of imaging studies had been enlarged. [Line 9-27, Page 4]

3. what did the authors mean with neurobehavioral stimuli? In sex research there a lot of experimental designs. Please explain.

The 'neurobehavioral stimuli' in Rationale for review section indicated visual erotic stimuli. This expression had been revised. [Line 14, Page 4]

4. Objectives: "Furthermore, this review also aims to synthesize the probable correlations between these altered cerebral regions and the clinical variables." Please reformulate this sentence. Maybe it 'd more correct to write about the statistical differences observed in some brain regions regarding the bold signal (fMRI) or in the volume.

The expression of this sentence had been revised in Objectives section. [Line 10-14, Page 5]

5. In the text the authors did not mention the eventual metanalyses performed on behavioral /psychometric /hormonal data included in the imaging studies. Maybe it is important to explain the inter-studies variability.

The value of the clinical characters (including behavioral /psychophysiological data) will be extract in Data collection progress [Line 27-29, Page 8], and they may be used to explain the inter-studies variability in data synthesis. [Line 17-18, Page 9]

6. Several functional imaging studies collected also the genital responses. Some studies collected also heart and respiratory rates. These psychophysiological data are important, overall, in the distinction between general arousal and sexual arousal and are important for pED.

The behavioral /psychophysiological data are important to assess the condition of patients in functional imaging studies, and we complemented these items at Outcome measures, Data collection and Outcomes and prioritization section. [Line 10-11, Page 7; Line 28, Page 8; Line 16, Page 9]

7. According to me it is difficult to compare results from "task-fMRI"(for example) and rs-fMRI studies. Please explain In which way different results (form rs or ICA, tasks and graph theory) could be compared.

Results from task-fMRI and rs-fMRI studies will not be 'compared', these results will be integrated separately according to the task /resting design and modalities of neuroimaging data. If data feasible, findings observed at resting-state imaging studies will be synthesized in the mate-analysis. [Line 15-18, Page 10]

8. "Again, the inter-rater reliability will be assessed by kappa value."- Please, specify the statistical test (Cohen and the range values).

The kappa coefficient will be calculated with Cohen's Kappa with the threshold $k > 0.75$. [Line 9, Page 10]

9. Conclusion. The conclusion section is very limited.

The content of the conclusion has been complemented in some range. According to the published protocol [¹,²] and submission guidelines of BMJ open, the conclusion section is not very indispensable. So, conclusion section of this protocol is very limited.

¹. Oakley NJ, Kneale D, Mann M, et al Association between type 1 diabetes mellitus and educational attainment in childhood: a systematic review protocol BMJ Open 2018;8:e021893.

². Kenteu B, Fogang YF, Nyaga UF, et al Neuroimaging of headaches in patients with normal neurological examination: protocol for a systematic review BMJ Open 2018;8:e020190.

Response to Reviewer: 4

Comments & Answers:

- Looking at the study question and short description of the field, I guess conducting a meta-analysis based on the retrieved studies will be challenging, especially since the outcome is not (cannot) be clearly defined.

The primary outcome of this review is the altered brain regions, and the activity likelihood estimation (ALE) meta-analysis could be conducted only based the x,y,z coordinates of foci (peaks of the altered brain regions) and sample size of included studies (see User Manual by Singer ALE, <http://www.brainmap.org/ale/manual.pdf>). According to the manual, the biggest challenge for ALE meta-analysis is too fewer original studies to guarantee the reliability and validity of results. So, we mentioned at the Data Synthesis section that 'If feasible (17 or more resting-state studies are included), an activity likelihood estimation meta-analysis will be launched in the manuscript.' [Line 17-20, Page 10]

- The search methodology seems sound, although I would not put an end date on it (thinking that time flies and it could be useful to do an update close to submission)

We changed the publishing time restriction, and the time of searching will be restricted to the anticipated completion date of this review. [Line 16, Page 2; Line 19-20, Page 7]

- Study outcome: I don't think it is an optimal definition for the outcome, since you already claim that you will only look at "significant" altered cerebral regions. So you suppose there is a change, and you imply that you will not include studies not reporting changes. The statistical methods could be described in more detail, i.e how do the data look like and how will they be pooled?

Different from the ordinary cohort studies or RCTs which have relatively few outcomes, the neuroimaging studies usually have large numbers of outcomes (such as activation/ correlation of every brain regions /voxels). So, almost all the neuroimaging studies only reported the significantly changed regions and ignore areas without significant differences. As a result, systematic reviews of neuroimaging study will (have to) only choose the significant altered cerebral regions as the study outcome. [*1, *2]

*1. Lee I S , Wang H , Chae Y , et al. Functional neuroimaging studies in functional dyspepsia patients: a systematic review. *Neurogastroenterology & Motility*, 2016, 28(6):793-805.

*2. Haggstrom L , Welschinger R , Caplan G A . Functional neuroimaging offers insights into delirium pathophysiology: A systematic review[J]. *Australasian Journal on Ageing*, 2017.

- Some revisions of the language are required
The language had been edited.

- I would suggest to use the term men instead of males. Although correct English, men is more respectful towards study participants + it is a problem for adults.

The expression of 'males' had been changed to 'men' in the manuscript.

- What do you mean with professional assessor? Do you mean someone experienced with quality assessment scoring, or a professional working with individuals with ED?

The professional assessor means someone experienced with quality assessment scoring. The ambiguous expression had been corrected in the manuscript. [Line 4-6, Page 10]

- I am not a fan of using kappa statistics to grade correlation between reviewers, since one of both individuals will anyway be more careful in excluding articles than the other. Most important is that all eligible articles are identified. It could therefore be considered that the first stage(s) of screening are done by 1 researcher to remove all clearly irrelevant articles, and that from abstract or full-text level, the screening is done in parallel. But again, most important is that all relevant articles are maintained. The kappa coefficient is only used to describe the inter-rater agreement of two researchers, which could reflect the robustness of the eligibility criteria and quality assessment criteria in some degree.

Referred to Prof. Brusselaers's suggestion, we adjusted the selection process of records [Line 6-13, Page 8]. Moreover, in order to maintain all the relevant articles, we adopt double screening and any disagreement between the two literature reviewers will be discussed and reconsidered by a third reviewer.

- Some language editing is needed.
The language had been edited.

VERSION 2 – REVIEW

REVIEWER	Hong Yin Department of Radiology, Xijing Hospital Xi'an, Shaanxi China
REVIEW RETURNED	17-Jul-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.
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REVIEWER	Nicoletta Cera Faculty of psychology and educational science- University of Porto, Porto –Portugal
REVIEW RETURNED	04-Jul-2019

GENERAL COMMENTS	Appraisal: According to me the manuscript is much improved and I would like to congratulate the authors for this job. According to me, it is useful to have protocol-articles that could help to perform studies (meta analytic in this case). I have only 2 concern: 1) the English language needs to be revised and corrected from a native speaker. 2) I ask more relevance to the previous models, used and developed to explain pED. This is crucial.
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VERSION 2 – AUTHOR RESPONSE

Response to Reviewer: 3

Comments:

1. The English language needs to be revised and corrected from a native speaker.
2. I ask more relevance to the previous models, used and developed to explain pED. This is crucial.

Answers:

1. The language had been edited by a professional copyediting company.
2. We strongly agreed with the reviewer's comments. The well-designed ED-related models were useful to explain the neurobiological underpinning of abnormal behaviour in patients with ED. Therefore, the importance of ED-related cognitive-behavioural models had been further emphasized in this protocol. In Data collection section, we will specially collect the data of cognitive-behavioural

models (Line 24, Page 8), and in the Data Synthesis section, we will pay special attention to synthesis the results of cognitive-behavioural models. (Line 15, Page 10)