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Systematic Review

Do Psychogenic Erectile Dysfunction and Premature Ejaculation Share a Neural Circuit? Evidence from a fMRI Systematic Review and Meta-Analysis

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Abstract: Background: Several functional magnetic resonance imaging (fMRI) studies investigated the brain correlates of psychogenic erectile dysfunction (PED) and premature ejaculation (PE), representing the most common sexual dysfunctions in men. These studies allowed a wide set of brain regions in PED and PE patients when compared to healthy men. In the present meta-analysis, we aim at assessing the presence of homogeneity in the cerebral underpinnings of PED and PE. Methods: Following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and after the electronic search, duplicate removal and the application of pre-exclusion criteria, nine PED and ten PE studies were considered eligible with a Cohen's k of 0.84 and 0.75, respectively. The effect sizes of the sociodemographic and psychological/urological dimensions were calculated. We extracted brain clusters from the retrieved studies, comparing patients and controls, and we calculated brain maps with Seed-Based D Mapping software. Results: We found a homogenous involvement of the frontal gyrus and insula in both dysfunctions, suggesting a common network. Conclusions: The anterior insula plays a key role in the processing of emotional features of stimuli, while the posterior insula in interoceptive information is relevant for sexual response. The prefrontal and inferior frontal cortices are important for sexual inhibition/disinhibition.

Keywords: fMRI; genital response; psychogenic erectile dysfunction; premature ejaculation; meta-analysis; resting state; effect size; homogeneity map

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1. Introduction

During the last few years, the neuroscientific community paid a growing interest to psychogenic erectile dysfunction (PED) and premature ejaculation (PE), which represent the most common sexual dysfunction in men. According to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5), PED is characterized by the difficulty in achieving and maintaining an adequate erection for vaginal intercourse, with a considerable decrease in penis rigidity, due to psychological factors [1].

Despite the DSM definition, PED has a multifactorial etiology comprising social, psychological, and biological factors that are mainly due to the accessibility of phosphodiesterase type 5 inhibitors (PDEi5) treatment and fertility [2,3] All of these factors can interact to affect the quality of life of the patients with PED. For example, the pharmacokinetics, pharmacodynamics, safety, and tolerability of sildenafil (PDEi5) can be altered in cigarette

smokers [4]. Among the psychosocial factors, relational distress, higher levels of perfectionism, neuroticism, and somatization were considered in PED patients [2]. Other factors are depression and anxiety. According to Farre et al. [5] depression, anxiety, obsessive–compulsive disorder, and psychotic disorders negatively interfere with the erectile response in men [6].

Conversely, PE can be conceived as an ejaculation pattern that occurs approximately one minute after vaginal intercourse without satisfaction for the patient, with a duration of at least 6 months [1,7].

In Europe, PED prevalence is 19% in Germany, 49% in Spain, and 48% in Portugal [8,9]. In addition, PE has an occurrence of 31% in Southwest Asia [10], 27% in Korea [11], and 23% in Portugal [12].

Erection and ejaculation showed a closed association during sexual intercourse or masturbation. According to preclinical studies [13], erection and ejaculation are independent events and erection is not a necessary condition for ejaculation. Ejaculation comprises three main phases: emission, expulsion, and orgasm [14,15]. Emission and expulsion occur throughout a coordinated process between the central nervous system and the autonomic nervous system at the spinal level [14,15]. This coordination involves the interplay between dopamine and serotonin that inhibits the sexual response throughout different brain regions [16,17].

Thus, at different levels, PE and PED negatively affect the sexual response, allowing the patient to have an unsatisfactory sexual experience. More specifically, PE and PED can negatively affect normal sexual inhibitory processes. Özdemir [18] hypothesized PE as an impulse control disorder (ICD) due to the inability to control ejaculation. Indeed, PE patients have a short latency in intravaginal ejaculation latency time (IELT) and can avoid sexual intercourse, considered as unsatisfactory due to partner' distress and frustration [19]. In addition, PE symptoms may be secondary to PED [20] suggesting that PE and PED can share a set of mechanisms.

Recently, functional magnetic resonance imaging (fMRI) allowed studying the brain correlates underlying of the sexual arousal and sexual inhibition [21–23]. In particular, Stoléru and colleagues [24,25] conceived the male sexual arousal as a complex process involving cognitive, emotional, motivational, and hormonal components. The authors also stated that inhibitory processes affect the components of sexual arousal.

The brain regions that exert inhibitory control over the sexual response are the temporal lobes, the left lateral orbitofrontal cortex (OFC), the caudate nucleus, and the caudal anterior cingulate cortex ACC [24,25]. Despite this inhibitory role, the OFC and ACC are also involved in the reward processing during the appraisal of the stimulus attractiveness [26,27]. These regions can modulate sexual arousal through the mediation of the responsiveness to erotic content [28,29]. The ventral striatum is also involved in reward processing, throughout the prediction and the level of the expectation of the reward [30,31]. According to the multi-component model, in PE, direct inhibition of one or more components may result in shortening the latency of ejaculation. Whereas PED should be the result of selective inhibition of the cognitive component responsible for the sexual stimuli appraisal.

On the other hand, Georgiadis and Kringelbach theorized a three-phase cycle model of sexual response including an expectation, a consummation, and a satisfaction phase [26,32]. Sexual inhibition is present in the satisfaction phase, immediately after the orgasm. Thus, the abnormally high activity in the prefrontal and superior parietal lobe can block the shifting between the expectation phase and the consummation phase. It is possible that in PE, this shift occurs faster than normal sexual response, through a hypo activity of the areas involved in the sexual-expectation network. Differently in PED, the shifting does not occur across the stages due to hyperactivity of the frontal, parietal, and temporal areas.

Despite PE and PED can be considered the most common male sexual dysfunction, to date no fMRI studies directly compared PE and PED patients' brain responses. Thus, the present meta-analysis aims at comparing PE and PED fMRI previously published study

results. In particular, we aim at investigating the brain regions associated with PE and PED and the presence of a joint neural circuit responsible for the aberrant sexual response. Moreover, we aim at testing the role played by brain regions, such as frontal, parietal, and temporo-limbic regions, in sexual inhibition in premature ejaculation and psychogenic erectile dysfunction.

2. Materials and Methods

2.1. Eligibility Criteria

The present meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33]. The research question followed the PICO strategy protocol [33]. To assess the eligibility of the studies, inclusion, and exclusion criteria were defined regarding the design, population, intervention, and study topics (Appendix A).

Figure 1 presents flow charts showing the process for study selection.

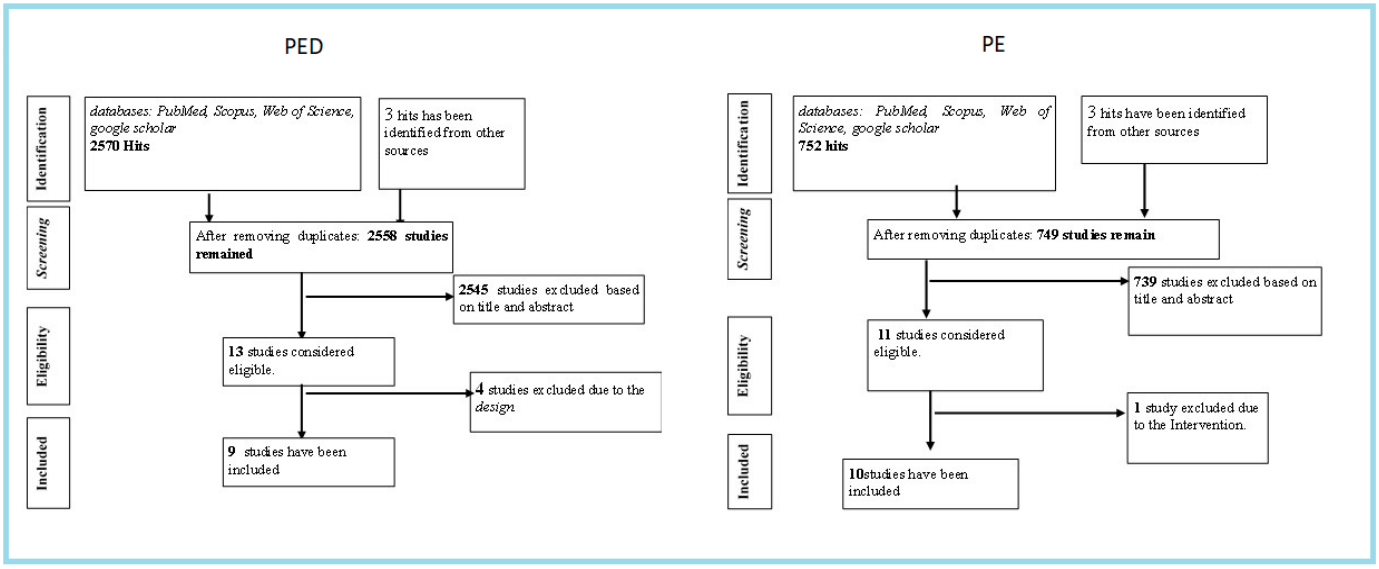

Figure 1. The figure depicts on the **left** side the flow chart of the selection process for PED studies and on the **right** side, the process for the PE studies.

2.2. Search Strategy

The present meta-analysis is divided into three distinct phases. In the first phase, to determine the eligibility of the studies, we inspected the results of the electronic search. A comprehensive search of published studies, with no time limit, was performed in PubMed, Scopus, Web of Science, and Google Scholar using the keywords "fMRI" AND "Psychogenic Erectile Dysfunction" OR "Psychogenic ED" OR " Neuroimaging" AND "fMRI" AND "premature ejaculation" and the Boolean search operators (AND) and (OR) (Appendix A).

After duplicate removal, we obtained 2558 PED studies. The titles and abstracts were evaluated according to the inclusion/exclusion criteria (Table 1).

Hence, 13 studies were considered eligible. Similarly, after duplicate removal, we obtained 749 PE studies. In addition, the titles and abstracts were examined in accordance with eligibility criteria and 11 PE studies were eligible.

Two researchers carried out this process independently. Nineteen studies were included, of which nine were PED and ten PE (Figure 1). In addition, the studies were read, assessed for the potential risk of bias, and the brain clusters were extracted. We assessed the overall quality of the studies, and the risk of bias, using the Newcastle–Ottawa quality assessment Scale case–control studies (NOS) [34]. NOS consists of three domains: selection, comparability, and exposure. Therefore, NOS assigns a maximum of nine stars to the studies with a low risk of bias [34] Table 2.

Table 1. Inclusion and exclusion criteria for the selected studies.

Inclusion Criteria	Exclusion Criteria
	Design
• Experimental studies	• Comparison with other patient populations • Sexual disfunctions (different from PE and PED). • Structural or morphological MRI studies
	Population
• Men	• Animals • Neuropsychiatric patients • Elderly people, women, children, adolescent, transsexual people.
	Intervention
• BOLD fMRI • Sexual stimuli	• Other neuroimaging techniques (i.e., PET; SPECT) or EEG.
	Topic
• Sexual behavior • Sexual dysfunctions • Brain activation • Brain activity	• Compulsive sexual behavior • Hypersexual behavior • Paraphilias.

Abbreviation: BOLD = blood oxygen level dependent; PET = positron emission tomography; SPECT = single-photon emission computerized tomography; EEG = electroencephalography.

Table 2. Classification of the studies according to the Newcastle–Ottawa scale case–control studies.

Psychogenic Erectile Dysfunction Studies			
Source	**Selection**	**Comparability**	**Exposition**
Cera et al., 2012	****	**	**
Cera et al., 2014	****	**	**
Chen et al., 2017	****	**	*
Jin et al., 2018	****	**	**
Liu et al., 2015	****	**	**
Montorsi et al., 2003a	***	–	*
Montorsi et al., 2003b	***	–	*
Wang et al., 2017	****	**	**
Yin et al., 2020	****	**	***
Premature Ejaculation Studies			
Source	**Selection**	**Comparability**	**Exposition**
Chen et al., 2020a	****	**	**
Chen et al., 2020b	****	**	***
Gao et al., 2020a	***	**	***
Gao et al., 2020b	***	**	**
Geng et al., 2021	***	**	**
Lu et al., 2018	***	**	***
Xu et al., 2019	***	**	***
Yang et al., 2018	***	**	***
Zhang et al., 2017	***	**	**
Zhang et al., 2020	****	**	**

NOS scale [29] is composed of three domains: selection, comparability, and exposition. * Indicates the rating score for each domain as assigned to each included study. Selection: max ****; comparability: max **; exposure: max ***.

2.3. Socio-Demographic and Behavioral Data Analysis

In the second phase of the meta-analysis, the homogeneity of the socio-demographic and behavioral reported results were analyzed. Effect sizes and Hedges g values were

calculated by means of Prometa-3 software (vers.3.0; Available at: https://idostatistics.com/prometa3; Accessed on 15 September 2020).

2.4. Brain-Clusters Data Extraction

In the third phase of the meta-analysis, we inspected the tables of the cluster coordinates of all included studies, and we extracted the statistical values. The analysis was performed using Seed-Based D Mapping (SDM— Available at: https://www.sdmproject.com/; Accessed on 15 September 2020) [35], which allows us to make inferences about neuroimaging studies [36]. SDM (vers. 6.21; https://www.sdmproject.com; Accessed on 15 September 2020) integrates the effect size and re-creates the activation maps using the coordinate peaks and their statistical values [36,37]. This allows the calculation of a 3D image of the effect size of each study.

Following the indications provided by Albajes-Eizagirre and colleagues [35], the peaks and t-values of the coordinates of the studies were first extracted. After the extraction of the effect sizes, these values were preprocessed, allowing the estimation of the potential higher and lower limits of the voxels, corresponding to the positive and negative threshold, respectively. Then, to readjust the voxels to the original space, a Gaussian kernel filter was calculated showing the effect sizes according to the intensity of the between-voxel correlation [38], following the truncated normal distribution. The maximum likelihood estimation (MLE) of the limits is transformed into parameters in which the effect sizes of the adjacent voxels must be positively correlated [36].

An anisotropic kernel-smoothing filter applied to the variance values of each voxel that follow a spatial covariance [35] performs the approximation to the truncated distribution. Then, the images of the single studies are a posteriori imposed together with the subjective permutations, representing the input to the group analysis for each study [36]. Despite advice from Radua and Mataixcols [36] to calculate and report uncorrected and corrected p values results, it was not possible to calculate the corrected *p*-value due to the low number of included studies in the present meta-analysis.

However, Radua and Mataixcols [36] recommend a *p*-value of 0.005 uncorrected as a reasonable threshold. To assess the robustness of between-group results, Jackknife sensitivity analyses were implemented, and the heterogeneity analyses were carried out using the Q statistic [37]. The calculation of the potential publication bias was provided by the Egger test implemented in SDM [38]. Due to the different study designs, we calculated five different SDM maps.

3. Results

3.1. Characteristics of the Included Studies

Table 3 shows the characteristics of the included studies. The selected studies were published from 2003 to 2021 and conducted in China (79%, n = 15) and Italy (21%, n = 4). Regarding the study designs, from the four studies that used a block design (21%), three studies used visual sexual stimulation (VSS), and one study used stop signal task. Thirteen studies used a resting state (68%) and two studies used a mixed design (11%). In total, data from 937 participants were collected, of which 369 were about PED and 568 were about PE. 124 brain activations were extracted, 70 from PED studies and 54 from PE studies. Cohen's k was 0.84 for PED studies with a 93% agreement between the two reviewers (N.C. and J.M.), whereas for PE studies it was 0.75 with 92% agreement. Both percentages indicate an almost perfect agreement [39].

Seventeen studies (89%) identified the recruitment site (i.e., hospital, Supplementary Material). Most of the studies reported the diagnostic guidelines for PED. However, two studies (11%) also applied the Mini International Neuropsychiatric Interview and DSM-IV criteria. Only three studies (16%) assessed the hormonal status of the participants. Moreover, the studies assessed anxiety and depression by means of the Self-Rating Anxiety Scale (SAS) [40] and the Self-Rating Depression Scale (SDS) [41], respectively. The sexual

function was measured using the International Index of Erectile Function (IIEF) [42,43], IELT [44], and premature ejaculation diagnostic tool (PEDT) [45].

Table 3. Sociodemographic characteristics, diagnostic criteria and tasks as reported in the included studies.

Source	Nr. Participants	Age	Diagnostic Criteria	Clinical Interview	Psychological Assessment (Tests)	Uro-Andrologic Assessment	Tasks
§ Cera et al., 2012	PED:17 HC: 19	PED: M = 34.3; SD = 11 HC: M = 33.6; SD = 11.5	DSM-IV	MINI	IIEF; SAI; SCL-90-R; STAI;BIS/BAS scale	Yes	VSS
§ Cera et al., 2014	PED:16 HC: 19	PED: M = 33.4; SD = 10.7 HC: M = 33.5; SD = 11.4	DSM-IV	MINI	IIEF; SAI; SCL-90-R; STAI;BIS/BAS scale	Yes	Long VSS
§ Chen et al., 2017	PED:24 HC: 26	PED: M = 29.8; SD = 4.62 HC: M = 32.81; SD = 8.38		Medical Clinical anamnesis.	IIEF; HAM-A; HAM-D	Yes	Resting state
§ Jin et al., 2018	PED: 26 HC: 26	PED: M = 26.8; SD = 5 HC: M = 28.5; SD = 3.2		Neuropsychiatric anamnesis; Sexual/psychosocial interview	IIEF;SAS;SDS	Yes	Resting state
§ Liu et al., 2015	PED: 27 HC: 27	PED: M = 33.22; SD = 5.92 HC: M = 31.41; SD = 5.82		Medical Clinical anamnesis	IIEF; QEQ; SEARQ	Yes	Resting state
§ Montorsi et al., 2003	PED:8 HC: 4	PED: M = 43; SD = N/A HC: M = 25; SD = N/A		Neuropsychiatric anamnesis;	N/A	Yes	VSS
§ Montorsi et al., 2003	PED:8 HC: 4	PED: M = 49; SD = N/A HC: M = 25; SD = N/A		Neuropsychiatric anamnesis;	N/A	Yes	VSS
§ Wang et al., 2017	PED: 27 HC: 27	PED:M = 26.58; SD = 4.89 HC: M = 28.39; SD = 3.53	DSM-5	Neuropsychiatric anamnesis; Sexual/psychosocial interview	IIEF; SAS; SDS	Yes	Resting state
§ Yin et al., 2020	PED: 31 HC: 24	PED: M = 13.97; SD = 3.6 HC: M = 22.21; SD = 0.98		Neuropsychiatric anamnesis; Sexual/psychosocial interview	IIEF; QEQ; SEARQ; SAS; SDS	Yes	Resting state
♦Chen et al., 2020	PE:17 HC:23	PE: M = 22.88; SD = 0.99; HC: M = 23.26; SD = 0.81		Medical Clinical anamnesis.	IIEF; IELT; PEDT	N/A	Resting state
♦Chen et al., 2021	PE:17 HC:24	PE:M = 21.47; SD = 0.62; HC: M = 21.72; SD = 0.74		Medical Clinical anamnesis.	IIEF-5; PEDT	N/A	Resting state
♦Gao et al., 2020(a)	PE:47 HC: 30	PE:M = 31.3; SD = 4.83 HC: M = 31.10; SD = 2.88		Medical Clinical anamnesis	IIEF-5; IELT PEDT; SAS; SDS	N/A	Resting state
♦Gao et al., 2020(b)	PE:45 HC: 37	PE:M = 30.90; SD = 5.31 HC:M = 30.84; SD = 3.23		Medical Clinical anamnesis	IIEF-5; IELT PEDT; SAS; SDS	N/A	Resting state
♦Geng et al., 2021	PE: 44 HC: 31	PE: M = 23.95; SD = 0.11 HC: M = 24.29; SD = 0.24		Medical Clinical anamnesis	IIEF-5; IELT; SAS; SDS	N/A	Resting state
♦Lu et al., 2018	PE:20 HC:15	PE:M = 27.95; SD = 4.52 HC: M = 27.87; SD = 3.78			IIEF-5; IELT; CIPE-5	N/A	Resting state
♦Xu et al., 2019	PE:20 HC:15	PE:M = 30.52; SD = 5.06 HC: M = 31.33; SD = 2.77			IIEF-5; IELT PEDT;	N/A	Resting state
♦Yang et al., 2018	PE:20 HC:15	PE:M = 30.52; SD = 5.06 HC: M = 31.33; SD = 2.77			IIEF-5; IELT PEDT;	N/A	Resting state
♦Zang et al., 2017	PE:20 HC:15	PE:M = 27.95; SD = 4.52 HC: M = 27.87; SD = 3.78			IIEF-5; IELT; CIPE-5	Yes	VSS Resting state

Table 3. *Cont.*

Source	Nr. Participants	Age	Diagnostic Criteria	Clinical Interview	Psychological Assessment (Tests)	Uro-Andrologic Assessment	Tasks
♦Zhang et al., 2020	PE:25 HC:21	PE:M = 30.44; SD = 5.59 HC: M = 32.29; SD = 6.60			PEDT; BDI	N/A	Resting state

§ Indicates PED studies. ♦ Indicates PE studies. Abbreviations: IIEF-5 = International Index of Erectile Function; PEDT = premature ejaculation diagnostic tool; BDI = Beck Depression Inventory; IELT = Intravaginal Ejaculation Latency Time; SAI= Sexual Arousal Inventory; SAS = Self-Rating Anxiety Scale; SDS = Self-Rating Depression Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; BIS/BAS scale = Behavioral Inhibition/Behavioral Activation Scale. CIPE-5 = Chinese Index of Premature Ejaculation-5; SEARQ = Self-Esteem and Relationship Questionnaire; QEQ = Quality of Erection Questionnaire; SCL-90R = Symptom Checklist-90-R; MINI = Mini International Neuropsychiatric Interview; STAI= State Trait Anxiety Inventory. HAM-A= Hamilton Anxiety Rating Scale; HAM-D= Hamilton Depression Rating Scale.

Three studies (16%) reported the diagnosis of PE according to the International Society for Sexual Medicine (ISSM) guidelines; with the IELT within 1 min and the PEDT score greater than 11. One study (5%) applied DSM-5 criteria. One study (5%) did not mention ISSM criteria. One study (5%) carried out a diagnosis with the result of the IELT within 1 min from the beginning of the sexual activity, an IIEF-5 total score major than 21, with a PEDT total score >11 and being in a stable heterosexual relationship of at least 6 months. Two studies (11%) did not report PEDT total score results. A study (5%) did not report PEDT total score results and ISSM criteria.

3.2. Sociodemographic Results

The main reported sociodemographic variables were age and education in years. We considered PED and PE as a single group (53%; n = 499). The same procedure has been applied to the control group (47%; n = 438). The mean age of the patient group is 26 years (S.D = 11.72), while the mean age of the control group was 23 years (SD = 8.5—Table S1).

Age showed heterogeneous results for the patients and control group (p = 0.000), no significant differences in effect size (p = 0.123) and sensitivity analysis for each study (Table S1), and the absence of publication bias in this variable (p = 0.752). Despite a significant difference observed for the effect size of education in years (p = 0.005), we found homogeneous results and no publication bias (p = 0.503; p = 0.183, respectively).

3.3. Behavioral Results

Most of the included studies reported results for anxiety and depression as measured by SAS (32%; n = 6) and SDS (32%; n = 6). Moreover, sexual function was measured by IIEF-5 (84%; n = 16), IELT (42%; n = 8), and PEDT (28%; n = 5—Table S1). Seventeen studies (89%) were considered for the analysis of effect size and publication bias. PED and PE patients and controls are significantly different in the SAS total scores (p = 0.000—Table S1), and heterogeneous (p = 0.000 Table S1) with a significant result for publication bias (p = 0.016—Table S1). SDS showed a global significant effect size (p = 0.000—Table S1) and a significant level of heterogeneity (p = 0.000; p = 0.006). The reported resulting scores of IIEF showed a significant effect size in total (p = 0.004) highlighting significant differences between the patient and the control group.

In addition, the two groups were heterogeneous (p = 0.000; p = 0.112) with no publication bias. Moreover, the reported resulting scores for IELT showed a significant effect size (p = 0.000), highlighting a between-group difference, with heterogeneity (p = 0.000) in the sample (Table S1) and no publication bias p = 0.112—Figure 1 and Table S1). For the reported PEDT results, the effect size shows a between-group difference (p = 0.001; p = 0.000; respectively, Table S1, Figures S1 and S2—Supplementary Materials), with a significant Egger test result (p = 0.000). Two PED studies reported subjective sexual arousal result scores (11%). Since two studies did not report the sociodemographic and behavioral results, we only considered seventeen published studies for this meta-analysis.

3.4. Homogeneity Maps Results

Homogeneity maps results are displayed in Table 4.

Table 4. Talairach coordinates Z and P values of the clusters as calculated for each map.

Cluster	Hemisphere	Coordinates (X, Y, Z)	Z Values	*p* Values	Nr. Voxels	BA
Global Map: Blobs ≥ 234 voxels Z ≥ 2.576; peaks Z ≥ 3.142.						
Anterior Prefrontal cortex	L	0, 52, 13	3.996	0.000	234	10
Anterior Prefrontal cortex	R	−4, 28, −10	3.142	0.000	305	11
Global Map: Blobs ≥ 3 voxels Z ≤ −2.577; Peaks Z ≤ −2.711						
Posterior insula/claustrum	L	−34, −7, 10	−3.442	0.000	176	13
Inferior frontal gyrus (Broca's Area)	R	43, 10, 11	−3.292	0.000	53	44
Inferior frontal gyrus, pars triangularis	L	−51, 34, 9	−2.732	0.003	16	45
Dorsal anterior cingulate cortex	R	6, 0, 37	−2.856	0.002	13	24
Anterior prefrontal cortex	R	19, 57, −6	−3.078	0.001	12	10
Task Map: Blobs ≥ 215 voxels Z ≥ 2.577; peaks Z ≥ 3.611.						
Anterior prefrontal cortex/ Ventromedial Prefrontal cortex	L	−2, 52, 17	3.611	0.000	215	10
Resting-State Map: Blobs ≥ 45 voxels Z ≤ −2.576; peaks Z ≤ −3.417						
Insula	R	47, 6, 0	−5.504	0.000	1678	13
Insula	L	−36, −7, 8	−4.245	0.000	404	13
Temporal pole	L	−41, 11, −12	−3.560	0.000	109	38
Anterior Prefrontal cortex	R	19, 57, 0	−3.417	0.000	45	10
PED Map: Blobs ≥ 1 voxel Z ≥ 2.578; peaks Z ≥ 2.599.						
Anterior Prefrontal cortex	L	−2, 52, 13	3.253	0.000	122	10
Orbitofrontal cortex	L	−6, 27, −12	2.909	0.001	39	11
Anterior insula	L	−40, 12, 1	2.864	0.002	22	13
Anterior Prefrontal cortex	L	−2, 55, 22	2.643	0.004	2	10
Ventromedial Prefrontal cortex	L	−8, 20, −9	2.599	0.004	2	25
PE Map: Blobs ≥ 54 voxels Z ≤ 2.579; peaks Z ≤ −3.279						
Posterior cingulate cortex/retrosplenial cortex	R	0, −38, 36	3.279	0.000	54	23
PE Map: Blobs ≥ 256 voxels Z ≤ −2.576; peaks Z ≤ −3.718						
Anterior insula	R	45, 8, −6	−5.102	0.000	849	13
Posterior insula	L	−40, −6, 6	−4.685	0.000	583	13
Orbital part of inferior frontal gyrus	L	−39, 13, −9	−4.520	0.000	453	47
Orbital part of inferior frontal gyrus	L	−49, 33, 2	−3.528	0.000	195	47

Abbreviation: BA = Brodmann Area; R = right; L = left.

Global map. The global map included all the clusters resulting from PED and PE studies (73%; n = 14) showing significant differences between the studies ($Q_{(13)}$ = 44.419; p = 0.000; t = 0.193—Table S2). We observed positive homogeneity in the left medial superior frontal and right orbito-medial region and a negative homogeneity in the left posterior insula, right inferior frontal gyrus, right orbital frontal gyrus, right anterior cingulate cortex, and left inferior frontal gyrus.

Task map. A second map has been calculated for all the studies that reported a task (16%; n = 3), composed of one PE study (33%) and 2 PED studies (67%) and showing a homogeneous cluster in the left medial superior frontal gyrus ($Q_{(2)}$ = 0.009; p = 0.995; t = 0.000—Table S2).

Resting-state map. The resting-state map, including seven PE studies (64%) and 4 PED studies (36%), showed significant heterogeneity ($Q_{(10)}$ = 34.583; p = 0.000; t = 0.309—Table S2). A negative homogeneity was observed in the right anterior and left posterior insula and in the left temporal pole.

PED map. The analysis of the PED map ($Q_{(5)}$ = 7, 057; p = 0.216; t = 0.040), showed significant homogeneity involving an extensive cluster in the frontal cortex and anterior insula (Table S2).

PE map. The PE map showed heterogeneous results ($Q_{(7)}$ = 43.156; p = 0.000; t = 0.253—Table 3). The right middle and left posterior insula and the left orbital, opercular, and triangular parts of the frontal gyrus showed negative homogeneity values (Table S2). Four studies, given their methodological characteristics, were excluded from this analysis.

Figure 2 shows SDM map results.

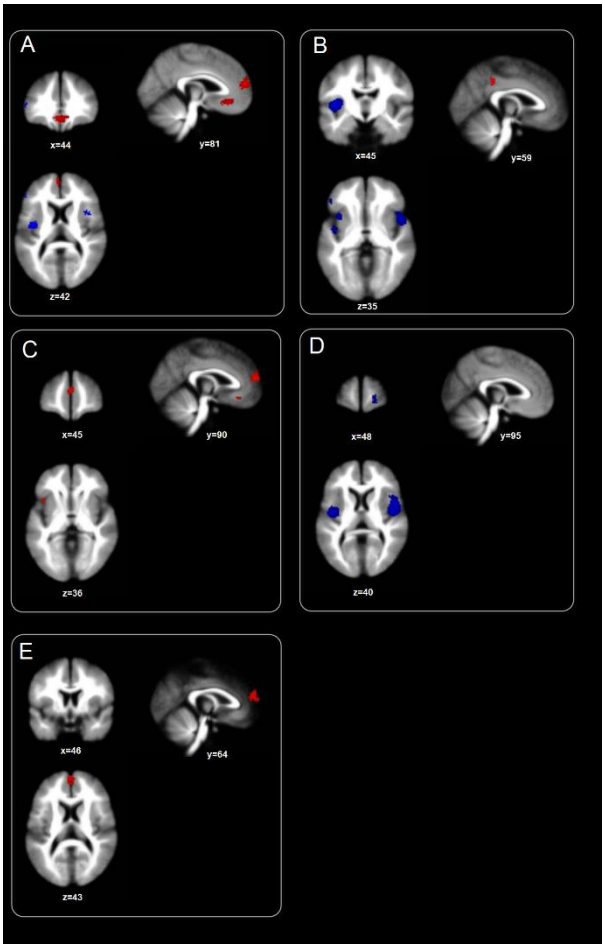

Figure 2. The figure depicted the meta-analysis results according to the subdivision performed and described in the methods. (**A**) Global results in which all the studies have been considered; (**B**) PE studies; (**C**) PED results; (**D**) resting state studies (**E**) task-based studies. Maps are in neurological convention and are over-imposed on MNI templates.

4. Discussion

The aim of the present meta-analysis was to study the brain activity associated with psychogenic erectile dysfunction and premature ejaculation, as reported by previously published fMRI studies. Despite PED and PE showing a different impairment of sexual context-evoked genital response, our results showed the presence of a common neural substrate underlying the two sexual dysfunctions.

In the global map, describing homogeneous foci resulting from the PED and PE studies, we observed a broad involvement of the superior and inferior frontal gyrus, posterior insula, and pregenual cingulate cortex. In particular, the left insula showed a constant homogeneity in the four maps. Otherwise, in the task map, a cluster was found in the superior frontal gyrus. The PED map shows the involvement of the left anterior frontal cortex, left anterior insula, and left orbitofrontal cortex. The PE map included the right posterior cingulate cortex, right middle and left posterior insula, and left orbital frontal gyrus.

In all of the maps, homogeneity in the insula represented the most prominent result. Despite the anterior and posterior insula playing a key role in the wanting and liking phase of sexual response, the role of insular sub-regions in the sexual response is still not clear [32,46]. The insula shows lateralization in the processing of the affective state. Indeed, the left insula usually elaborates positive states, while the negative states are processed in the right insula [47]. The anterior insula is involved in performance monitoring and

focused attention to negative stimuli causing anxiety [48,49]. Moreover, the insula is part of the dopaminergic and oxytocinergic systems that are relevant for sexual response and sexual motivation [50–53].

In PED, we have found a fronto-insular network, reflecting a possible role in inhibition and in hypervigilance. The anterior insula is a key region responsible for the integration of sensory and autonomic inputs after stimuli appraisal. According to Stoleru et al. [54], OFC is involved in the appraisal [24,25] of the features of the sexual stimuli, in decoding their reward values and the subjective emotional experiences [54]. Therefore, OFC and the insular cortex have a strict relationship in emotion recognition. In this case, this bidirectional relationship between OFC and insula is preserved in PED, suggesting a normal integration between appraisal and emotion recognition in the patients. Additionally, the left ventromedial prefrontal cortex (vmPFC) was observed in the PED map.

Li et al. [55] highlighted the role played by vmPFC in the processing of self-referential information. This region is involved in managing the attention between external stimuli, inner thoughts, and mentalization [56,57]. Given that most of the studies that applied a task involved PED patients, vmPFC was also relevant in the task map. According to this result, it is conceivable that PED patients can show constant hypervigilance of the bodily state changes during the emotional processing of sexual stimuli. Furthermore, vmPFC can contribute to the inhibition of sexual response through the redirection of the attentional focus towards self-related thoughts, instead of external stimulation.

In PE, we observed foci in the right anterior, left posterior insula, left inferior frontal gyrus, and posterior cingulate cortex. The bilateral activation of the insula was related to the anticipation of uncertainty [58–60]. Thus, impulsivity is also related to a network including bilateral, inferior frontal gyrus, angular gyrus, and inferior parietal lobe [61]. Indeed, the inhibitory control of the behavior is strictly related to the activity of the inferior frontal gyrus [62,63]. Moreover, the posterior cingulate cortex (PCC) was observed in self-referenced processing and autobiographical memories [64]. PE showed a brain network that enables the integration of multimodal somatosensory inputs [65]. The presence of the interaction between the insula and IFG can be responsible for disinhibition, shortening the latency time of ejaculation. In addition, the effect of PCC, with the retrieval of autobiographical memories, can play a possible role in the reinforcement of the negative experience.

The global map showed homogeneity in the bilateral anterior prefrontal cortex, left posterior insula, right and left inferior frontal gyrus, and dorsal cingulate cortex. As discussed above, the anterior prefrontal cortex is related to the appraisal of the salience and subjective pleasantness of the stimuli. Therefore, the posterior insula plays a key role in the emotional component of sexual arousal [24,25], in the recognition and awareness of visceral alteration concomitant to arousal.

According to Georgiadis and Kringelbach [32], the posterior insula is present in the consummation phase. It is possible that aberrant crosstalk of the insula with other regions could result in the absence of sexual response in PED. Furthermore, ACC is present in distinct phases of the sexual response such as sexual drive [66], planning of motor behavior [67], and in reinforcement [68]. It is conceivable that in both dysfunctions, and at different levels, the prefrontal and inferior frontal cortex can negatively affect the sexual response. Indeed, in both dysfunctions, redirecting the attentional focus to the self-related processes can negatively affect the appraisal of the sexual stimuli.

The present meta-analysis studied only the brain clusters resulting from the comparison between patients and controls. This can represent a limitation of the present study. According to Moreno and colleagues [69], the publication bias, as assessed by means of Egger's test [70], is dependent on the number of studies included in a meta-analysis. Another limitation is the heterogeneity in the tasks and the experimental paradigms used in the included studies. Indeed, most of the PED studies used tasks and most of the PE studies used the resting state to study the brain activity in patients.

The present meta-analysis provides a starting point for future fMRI studies. Future studies could focus on the activity of the insula and prefrontal cortex using new techniques of data analysis, taking into account self-referential processes. However, the results here need to be carefully considered, since a greater and more homogeneous number of studies should be needed.

5. Conclusions

The purpose of this meta-analysis was to disentangle the common brain correlates of psychogenic erectile dysfunction and premature ejaculation. We found homogeneity in correspondence between bilateral insular cortices, in the medial and inferior upper frontal gyrus, suggesting a specific network in the sexual response of these two dysfunctions. The anterior insula can play a role in anticipating and decoding emotional stimuli, while the posterior insula in processing interoceptive information and bodily changes.

Moreover, the prefrontal cortex and inferior frontal gyrus are important for inhibitory control. Despite previous studies investigating the two dysfunctions, using different types of tasks and data analysis techniques, future multimodal neuroimaging studies, will provide new insights into the brain correlates of PED and PE.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app122111249/s1, PRISMA 2020 Main Checklist; Figure S1: Funnel plots for the publication bias (socio-demographic and psychometric tests results); Figure S2: Forest plot for the effect size and sensitivity; Table S1: Effect size, heterogeneity and publication bias for the sociodemographic and behavioral results; Table S2: Effect size for the five maps.

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Appendix A

PICO Worksheet and Search Strategy Protocol

1. Define your question using PICO by identifying: Patient/Problem, Intervention, Comparison group and outcome:

Patient/Problem: Patients with psychogenic Erectile Dysfunction, Patients with Premature Ejaculation
Intervention: fMRI
Comparison: comparison of the patients with healthy controls
Outcome: brain regions activations
Write out your question: Do psychogenic erectile dysfunction and premature ejaculation share a neural circuit?

2. Type of question/problem:

Circle one: Therapy/Prevention/Diagnosis/x Etiology/Prognosis

3. Type of studies/publications to include in the search:

Check all that apply:

☐ x Meta-analysis ☐ x Systematic review
☐ Clinical practice guidelines ☐ Randomized controlled trial
☐ xResearch studies or articles ☐ Case report or series
☐ Research report or other grey literature

4. List main topics and alternate terms from your PICO question that can be used for your search: "experimental studies"; "men"; "fMRI BOLD"; "erotic stimuli"; "Sexual behavior"; "Sexual dysfunction"; "Brain region activity".
5. Write out your search strategy: "fMRI" AND "Psychogenic Erectile Dysfunction" OR "Psychogenic ED" OR" Neuroimaging" AND "fMRI" AND "premature ejaculation" Boolean search operators (AND) and (OR).
6. List any limits that may apply to your search: Gender: Male; Age: Adults; Year(s) of publication: 2003–2020; Language(s): English
7. List the databases you will search: Google Scholar, PubMed, Scopus, and Web of Science.

This form is adapted from: Miller, S.A. (2001). PICO worksheet and search strategy. US National Center for Dental Hygiene Research

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