

Review

Uncovering the role of sociodemographic factors in sex/gender differences in emotional brain activation: an SDM-PSI meta-analysis of fMRI studies

Paula Ariño-Braña^a, Rita Vieira^{b,c}, Carles Soriano-Mas^{d,e,f}, Joaquim Radua^{g,h},
Maria Picó-Pérez^{a,c,*}

^a Department of Basic and Clinical Psychology and Psychobiology, Jaume I University, Castellón de la Plana, Spain

^b Clinical Academic Center, Braga, Portugal

^c Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus Gualtar, Braga, Portugal

^d Department of Social Psychology and Quantitative Psychology, Institute of Neurosciences, Universitat de Barcelona - UB, Barcelona, Spain

^e Psychiatry and Mental Health Group, Neuroscience Program Bellvitge Biomedical Research Institute - IDIBELL, L'Hospitalet de Llobregat, Spain

^f Network Center for Biomedical Research on Mental Health (CIBERSAM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

^g Imaging of Mood- and Anxiety-Related Disorders (IMARD) Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERSAM, Barcelona, Spain

^h Department of Medicine, Facultat de Medicina i Ciències de la Salut, University of Barcelona, Barcelona, Spain

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ABSTRACT

Introduction: The study of sex/gender (S/G) differences in neuroscience, particularly in emotional processing, has been hindered by methodological inconsistencies, often producing biased conclusions that overgeneralize brain differences between males and females. Moreover, many studies fail to consider how other sociodemographic factors interact with S/G to influence the brain. This study aims to address these gaps by investigating whether potential S/G effects in brain activation during emotion-evoking functional magnetic resonance imaging (fMRI) tasks are influenced by those factors.

Methods: This meta-analysis followed Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and was registered on PROSPERO. We searched for peer-reviewed studies on S/G differences in whole-brain activations during fMRI emotion-evoking tasks. Data analysis was conducted using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI). Subgroup analyses were performed based on the type of tasks and on race, and meta-regressions assessed the impact of age, education, and hormonal contraceptive use on the main effects.

Results: 63 studies were included for the meta-analysis, comprising a total of 5,436 individuals from the general population (2,635 females). The main meta-analysis showed no significant S/G activation differences at the whole-brain level. Subgroup analyses, however, revealed significant S/G differences depending on the type of task and the race subgroup, while meta-regression analyses showed significant associations between S/G effects and education and hormonal contraceptive use, with notable shifts in activation patterns across these variables.

Discussion: Our findings highlight the need for more complex, intersectional models that consider the dynamic interplay of biological, psychological, and social factors in shaping S/G differences in brain function and mental health.

1. Introduction

The study of sex/gender (S/G) differences has been key in advancing scientific research and healthcare across numerous fields (García-Sifuentes and Maney, 2021). Although usually overlooked in research, with females frequently excluded from clinical studies, research has increasingly demonstrated the importance of considering

S/G for advancing knowledge and promoting individualized care (Beery & Zucker, 2011; Clayton & Collins, 2014). In this regard, a substantial body of psychological and neuroscientific research has explored S/G differences in emotional processing (Kret & De Gelder, 2012; Whittle et al., 2011). This topic has attracted considerable interest due to the high global prevalence of emotional discomfort across the general population (Arcand et al., 2023), with a perceived lack of sufficient

* Corresponding author.

E-mail address: picom@uji.es (M. Picó-Pérez).

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resources to cope with demanding situations (Costa et al., 2021). S/G differences in resilience, susceptibility and prevalence of mood disorders are commonly reported, with females generally reporting higher levels of negative emotionality and negative arousal than males (Javaid et al., 2023; Swaab & Bao, 2020). However, despite this evidence, findings on S/G-related brain responses to negative emotions in the general population remain inconsistent (Gardener et al., 2013; McRae et al., 2008; Stoica et al., 2021).

Importantly, methodological concerns persist within the study of S/G in this domain. For example, the publication bias that prioritizes statistically significant results over null findings (Hines, 2020) can, in the long term, promote distorted interpretations of S/G differences regarding emotional processing and its associated brain correlates. Furthermore, there is methodological variability even in carefully designed studies (DeCasien et al., 2022), underscoring the need for systematic reviews and meta-analyses to reconcile these findings. In addition, S/G research is predominantly performed within a binary framework, comparing males versus females (Picó-Pérez et al., 2024). This framework is typical in neuroscience in general, despite growing recognition that "female"¹ and "male" brains exhibit considerable overlap and cannot be categorized into two separate groups (Joel, 2021). While common, this framework risks oversimplifying neural and behavioural complexities by viewing S/G differences as inherent, static traits (Joel, 2021; Rippon et al., 2014; Sanchis-Segura and Wilcox, 2024). It also overlooks the influence of sociodemographic factors that may modulate S/G similarities and differences, suggesting that the observed differences may be influenced by other interrelated factors in which S/G differences arise.

Thus, frameworks that capture S/G-related dimensions beyond binary categorization are needed (Fitsch, 2021; Wierenga et al., 2024), as well as considering other sociodemographic factors that might be intersecting with S/G effects. One of such factors is race². As mentioned by Vrana and Rollock (2002), emotional experience and expression are embedded within social structures. Consequently, variation across racial groups and their sociocultural contexts represents an important framework in emotion research. Given that S/G differences are also culturally influenced, previous literature has proposed that the joint examination of race and S/G may offer important insights into emotional processes. Besides, age might also play a significant role, since different emotionally salient stimuli arise depending on age, as well as the emotion regulation strategies used to tackle them (Charles and Carstensen, 2007; McRae et al., 2012). Importantly, this is not only influenced by biological factors (such as hormonal levels), but there may also be other relevant factors related to gender roles and socialization, that would differentially affect brain development at multiple stages (Moreno-Rius, 2019). Similarly, education, understood as cognitive enrichment and socioeconomic advantage, has effects on the brain (Kang et al., 2021; Vannucci et al., 2023), and educational resources could either reinforce or challenge gender norms and experience (Picatoste et al., 2023; Rotman & Mandel, 2023). For example, previous literature has reported inconsistent findings regarding the relationship between S/G, education, and emotional intelligence (Britwum et al., 2024), which aligns with our interest in examining how S/G and education interact in shaping emotional brain responses. Finally, previous literature has highlighted the impact of hormonal contraceptives use on mental health

and brain changes associated with mood regulation (Concas et al., 2022). Sexual hormones play a significant role in the human brain by influencing cortisol release and modulating brain regions involved in emotion regulation, further affecting neurotransmitter synthesis (Nasseri et al., 2020; Segarra et al., 2023). Thus, hormonal contraceptive use emerges as another relevant factor to explore in this context.

This meta-analysis seeks to investigate S/G differences in whole-brain activations during emotionally-evocative functional magnetic resonance imaging (fMRI) tasks (for the contrast of emotional versus neutral/baseline conditions), aiming to determine whether previously reported findings from individual studies reflect non-null effects. Additionally, it aims to examine how the selected factors, including race, age, education, and hormonal contraceptive use, as well as variability in task paradigms, may modulate these neural responses. We hypothesize that a general pattern of S/G significant differences in whole-brain activations during emotionally arousing conditions (versus neutral/baseline) will not emerge, while we expect the selected variables to reveal statistically significant modulations of whole-brain S/G effects.

2. Methods

This meta-analysis was conducted according to PRISMA guidelines (<http://www.prismastatement.org/>). The study protocol is publicly available in the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024508446). We also followed guidelines and recommendations for neuroimaging meta-analyses (Müller et al., 2018).

2.1. Literature search and selection criteria

We conducted the literature search across PubMed, Scopus, and ScienceDirect databases, focusing on peer-reviewed articles published in English between January 2005 and March 2025. This search targeted studies exploring S/G differences in whole-brain activations during fMRI emotion-evoking tasks. The aim was to include tasks that, although differing in paradigm, consistently engaged emotionally arousing affective processing, particularly in response to salient, aversive, or socially evaluative stimuli. Thus, the underlying process of interest consisted on the processing of emotionally salient and arousing information, despite variations in methodology. Keywords used included: ('sex' OR 'gender' OR 'sex differences' OR 'gender differences') AND ('fMRI' OR 'fMRI' OR 'neuroimaging' OR 'functional magnetic resonance imaging' OR 'functional imaging') AND ('emotion' OR 'emotional processing' OR 'emotional regulation' OR 'emotional elicitation' OR 'stress').

The studies listed under these keywords were then imported into Rayyan (<https://www.rayyan.ai>) for the first selection phase. This platform allowed for a first blinded, independent review by two researchers, with a third researcher resolving inconsistencies afterwards. For this preliminary screening, inclusion was based on abstracts, followed by a comprehensive full-text review of the studies included after the screening. Eligible studies were those examining whole-brain activation differences between males and females from the general population in response to emotionally evocative conditions versus baseline/neutral conditions. Studies were excluded if they were reviews, meta-analyses or non-articles (e.g., conference abstracts), lacked fMRI data, involved only animal models, had small sample sizes ($n < 10$ per group), did not employ emotionally evocative tasks, did not include a direct S/G comparison, did not include healthy³ subjects, did not perform the required statistical comparison (healthy females versus males in the

¹ To maintain uniformity throughout the article, we will solely employ the terms "female" or "male". However, we use the double-term "sex/gender" ("S/G"), in agreement with other authors (Bluhm, 2013), acknowledging that while sex and gender are separate concepts, their effects are intertwined, and isolating them is challenging with most study designs.

² By race we refer to a socially constructed classification used to divide humans into groups based on biased judgments of physical characteristics and appearance, and which have been historically politically driven and used to establish social hierarchies (Cardenas-Iniguez and Gonzalez, 2024).

³ By healthy we refer to subjects lacking a psychiatric diagnosis, which is how this term is commonly used in the context of mental health research, but this does not imply that subjects were necessarily healthy in all other unexplored aspects of their health.

emotion > neutral/baseline contrast) or their results were not reported at the whole-brain level, or the sample overlapped with other included studies.

Regarding the contrasts of interest, whenever possible, contrasts capturing negative/aversive affect relative to neutral conditions were retained, which are the most representative of this literature. As a result, most included studies involved negatively valenced, aversive, or stress-related experimental conditions (see Table 1). A limited number of studies combined negative and positive stimuli, or explored positive arousing stimuli alone (e.g. erotic stimuli); nevertheless, these were retained to ensure broad coverage of the existing literature. Sensitivity analyses were conducted to determine whether the inclusion of these studies influenced the results (see section 2.3.).

Following the full-text review, we contacted study authors to request data regarding the demographic variables of interest (race, age, education, and contraceptive use) and the original whole-brain statistical maps for the relevant contrast. When inclusion remained uncertain, or in cases of exclusion because of not performing the required statistical comparison or not reporting it at the whole-brain level, authors were contacted for additional information or unpublished data potentially meeting the inclusion criteria (see Fig. 1 for the literature search flow chart).

2.2. Data extraction

We extracted peak regional coordinates and t-statistics for the contrast of interest directly from the original manuscripts. Additionally, we obtained original brain statistical maps from seven independent datasets across seven separate studies (Chaudhary et al., 2023; Dan et al., 2019; Dong et al., 2022; Koch et al., 2019; Li et al., 2020; Merz et al., 2013; Min et al., 2023). These maps were subsequently reviewed to verify consistency with the results reported in the manuscripts. Sociodemographic data of interest were also gathered from all included studies (see Table 1).

For consistency in recording the statistical data, we standardised the sign of the t-statistic across all studies. Positive t-values indicated higher activation in females relative to males, while negative t-values indicated higher activation in males compared to females for the contrast of interest.

2.3. Data analysis

2.3.1. Main meta-analysis

The analysis was conducted using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI) software, version 6.23, which allows to test the statistical significance of results rather than assessing their convergence (<https://www.sdmproject.com/>; Albajes-Eizaguirre et al., 2019). It integrates both extracted brain statistical results (e.g., coordinates and peak t-values) and voxel-wise brain statistical maps to generate voxel-wise (random effects) effect size maps for the contrasts of interest (Radua et al., 2012, 2014). For studies with only peak coordinates available, the method imputes study images with realistic spatial covariance to cover uncertainty. The results are combined using Rubin's rules, producing a meta-analysis image for each dataset and, after multiple iterations, a final meta-analysis image is created by combining all datasets, accounting for both within-study variability and between-study heterogeneity. Further details of the SDM-PSI method have been published previously (Albajes-Eizaguirre et al., 2019).

The main meta-analysis aimed to compare whole-brain activation between females and males across the entire sample for the emotional versus neutral/baseline contrast. In addition, a sensitivity analysis was conducted assessing the potential impact of excluding those studies that did not exclusively employ negative stimuli. Statistical significance was defined at a voxel-level threshold of $p < 0.05$, corrected using Threshold-Free Cluster Enhancement (TFCE), with a minimum cluster extent (Ke) of 10 contiguous voxels. All results are reported in Montreal

Neurological Institute (MNI) coordinates.

2.3.2. Subgroup meta-analysis by type of task

Subgroup meta-analyses were performed to examine the potential influence of task heterogeneity. To this end, tasks were classified either as 'active' or 'passive'. 'Active' tasks were defined as those requiring participants' active engagement in a task under actual or perceived assessment/threat (i.e., performance-based or socially evaluative threat paradigms). In contrast, 'passive' tasks involved the presentation of emotional stimuli to the participants (e.g., negative and neutral images), without requiring active task performance. Moreover, a similar sensitivity analysis as for the main meta-analysis was performed for the passive subgroup meta-analysis, to determine the impact of excluding non-exclusively negative emotional stimuli. This was not performed for the active subgroup meta-analysis, as all active paradigms were considered to elicit negative arousal or emotional responses. Statistical significance was defined at a voxel-level threshold of $p < 0.05$, corrected using TFCE, with a minimum Ke of 10 contiguous voxels.

2.3.3. Subgroup meta-analysis by race

Further subgroup meta-analyses were conducted to examine the potential influence of race on S/G differences in whole-brain activations for the contrast of interest. To ensure sufficient statistical power, these analyses were only conducted when at least 10 studies were available per group. Since most samples comprised Caucasian participants, one subgroup meta-analysis included only samples with mostly Caucasian participants (> 50 %), while the other included samples with participants mostly of other races (> 50 %), which specifically comprised Asian, Latin, and/or African American (see Table 1 for detailed information on this regard). Statistical significance was again set at a voxel-level threshold of $p < 0.05$, TFCE corrected, with a minimum Ke of 10 contiguous voxels. Despite not achieving the minimum of 10 studies, since most samples of other races were composed of Asian participants (8 out of the 10 studies), we conducted a further exploratory subgroup meta-analysis limited to studies with primarily Asian samples (> 50 % Asian).

2.3.4. Meta-regressions

Meta-regressions were conducted to assess associations between the rest of the sociodemographic variables of interest (age, education, and hormonal contraceptives use) and the main meta-analysis outcome, namely whole-brain S/G differences for the contrast of interest (i.e. emotional versus neutral/baseline conditions). Meta-regressions were performed when we had access to at least 10 studies for each variable of interest, which was the case for all of them. Again, statistical significance was determined using a voxel-level threshold of $p < 0.05$, TFCE corrected, and a minimum Ke of 10 contiguous voxels was applied. In the case of age and education, the data was included as mean years, that is, mean age and mean years of education, from the whole sample. Importantly, females and males were matched on age and years of education in all studies that reported this information. Regarding the use of hormonal contraceptives, the data was included as the percentage of females using hormonal contraceptives.

2.4. Multiple comparison correction

To control for multiple comparisons across the seven planned analyses (i.e. four subgroup meta-analyses, and three meta-regressions), we applied a Bonferroni correction by adjusting the TFCE voxel-wise threshold from $p < 0.05$ to $p < 0.007$. This correction was not applied to the exploratory subgroup meta-analysis of primarily Asian samples, which was conducted post-hoc to check for the specificity of the "other races" subgroup meta-analysis. As such, results from this exploratory analysis should be interpreted with caution.

Table 1

Characteristics of the datasets included in the meta-analysis.

Study	Task	Contrast of interest	Sample N (females)	Race	Mean age ($\pm$ SD)	Education years ($\pm$ SD)	Hormonal contraceptives
Balters et al. (2023)	Validated Task – Microaggression videos	Gender-based microaggressions vs control videos	28 (16)	NA	37.74 ($\pm$ 6.94)	NA	NA
Beking et al. (2020)	NimStim set of Facial Expressions	Negative emotional expression vs circular expression match	41 (21)	NA	16.16 ($\pm$ 0.8)	NA	NA
Benson et al. (2012)	Rectal Distension	Pain induction vs resting state (no pain)	30 (15)	NA	25.75 ($\pm$ 6.05)	NA	100 %
Briceño et al. (2015)*	Facial Emotion Perception Test	Emotional faces vs animals	57 (19)	NA	46.68 ($\pm$ 7.63)	NA	NA
Butler et al. (2005)	Electrodermal Stimulation	Painful stimulation vs safe condition	23 (10)	NA	27.68 ($\pm$ NA)	NA	NA
Canterberry et al. (2016)	IAPS Images Presentation	Negative vs neutral images	20 (10)	Caucasian (70 %)	34.85 ($\pm$ 7.62)	16.15 ($\pm$ 3.08)	NA
Caseras et al. (2007)	IAPS Images Presentation	Negative vs neutral images	34 (17)	Caucasian (100 %)	29.74 ($\pm$ 8.17)	NA	NA
Chaudhary et al. (2023)	Hariri Picture Matching Task	Negative vs neutral images	30 (15)	Caucasian (71 %)	57.82 ($\pm$ 18.04)	16.17 ($\pm$ 2.55)	5.08 %
Chun et al. (2012)*	Emotional Vocalization Presentation	Emotional vs neutral prosody	46 (15)	Asian (100 %)	30 ($\pm$ 2.9)	13.8 ($\pm$ 2)	NA
Chung et al. (2016)*	MIST	Stress vs control	44 (25)	Caucasian (100 %)	25.36 ($\pm$ 3.35)	16.13 ($\pm$ 2.25)	0 %
Coenjaerts et al. (2022)*	IAPS Images Presentation	Emotional vs neutral images	98 (39)	NA	24.16 ($\pm$ 4.58)	NA	0 %
Colich et al. (2017)	Modified Hariri Emotion Label Task	Emotion labelling vs emotion match	45 (26)	NA	11.58 ($\pm$ 0.98)	NA	NA
Crozier et al. (2014)	Modified Emotion Oddball Task	Fear vs calm faces	86 (50)	Caucasian (56 %)	12.83 ($\pm$ 2.55)	NA	NA
Dahm et al. (2017)*	ScanSTRESS Task	Social stress vs control	40 (20)	NA	27.7 ($\pm$ 5.93)	NA	46 %
Dan et al. (2019)	Hariri Emotional Face Matching Task	Negative face match vs spatial orientation control task	24 (12)	Asian (93 %)	24.1 ($\pm$ 2.64)	14.08 ($\pm$ 1.65)	0 %
Derntl et al. (2010)*	Emotion Recognition Task	Emotion recognition vs resting state	48 (24)	Caucasian (100 %)	27.3 ($\pm$ 5.35)	16.1 ($\pm$ 2.4)	0 %
Derntl et al. (2012)*	Emotion Recognition Task	Emotional vs neutral faces	33 (17)	NA	24.6 ($\pm$ 3.43)	NA	NA
Domes et al. (2010)	Emotional Regulation Task	“Maintain” negative vs neutral images	243 (137)	NA	24.89 ($\pm$ 1.75)	NA	NA
Dong et al. (2022)*	MIST	Stress vs control	42 (22)	Asian (100 %)	20.94 ($\pm$ 3.21)	14.34 ($\pm$ 1.43)	NA
Felmingham et al. (2010)	Fear Perception Task	Fear vs neutral faces	20 (10)	NA	28.72 ($\pm$ 11.5)	NA	NA
Fine et al. (2009)	Emotional Face Images Visualization	Negative	35 (15)	NA (100 %)	21.86 ($\pm$ 1.71)	NA	NA
Geng et al. (2018)	Everyday Embarrassing Situation Pictures Visualization	Self vs other embarrassment	60 (31)	Asian (100 %)	21.86 ($\pm$ 0.33)	15.89 ($\pm$ 0.28)	NA
Goldfarb et al. (2019)	Stressful and Neutral Pictures Visualization	Stress vs neutral images	24 (12)	NA	28.48 ($\pm$ 9.45)	NA	NA
Han et al. (2008)	Threatening Situations Pictures Visualization	Threat detection vs gender identification	67 (31)	Asian (100 %)	21.34 ($\pm$ 1.42)	NA	NA
Henze et al. (2021)*	ScanSTRESS Task	Stress vs control	38 (19)	NA	23.06 ($\pm$ 2.88)	NA	100 %
Hofer et al. (2007)	Emotional Words and Nouns Visualization	Negative words vs control	125 (53)	NA	32.98 ($\pm$ 8.68)	14.06 ($\pm$ 2.58)	NA
Holz et al. (2016)	Hariri Emotional Face Matching Task	Negative face match vs spatial orientation control task	108 (64)	NA	NA	NA	NA
Im et al. (2018)	Emotional Face Images Visualization	Fearful vs neutral faces	24 (12)	NA	37.04 ($\pm$ 16.56)	NA	NA
Imaizumi et al. (2004)*	Emotional Prosody Phrases Listening	Emotional prosody vs resting	40 (20)	Asian (100 %)	24.7 ($\pm$ NA)	NA	NA
Karama et al. (2002)*	Erotic Films Visualization	Erotic vs neutral videos	20 (10)	NA	24.5 ($\pm$ 3.5)	NA	NA
Klein (2003)	IAPS Images Presentation	Negative vs positive images	40 (19)	NA	41.6 ($\pm$ 7.01)	NA	NA
Koch et al. (2007)	Nauseous and Neutral Ambient Air Odour Stimulation	Negative vs neutral stimulation	40 (20)	NA	31.92 ($\pm$ 10.6)	12.43 ($\pm$ 2.75)	NA
Koch et al. (2019)	IAPS Images Presentation	Negative vs neutral images	43 (23)	Caucasian (100 %)	40 ($\pm$ 10.05)	NA	45 %
Kogler et al. (2015)*	MIST	Stress vs control	80 (40)	NA	24.56 ($\pm$ 2.8)	NA	47.82 %
Kogler et al. (2017)*	MIST	Stress vs control	140 (73)	NA	24.55 ($\pm$ 3.65)	NA	NA
Kuhn et al. (2023)*	ScanSTRESS	Stress vs control	26 (14)	NA	23.15 ($\pm$ 3.26)	NA	100 %

(continued on next page)

Table 1 (continued)

Study	Task	Contrast of interest	Sample N (females)	Race	Mean age (± SD)	Education years (± SD)	Hormonal contraceptives
Lan et al. (2024)*	Nencki Affective Picture System Images Presentation	Emotional vs neutral images	970 (508)	Asian (100 %)	21.19 (± 2.10)	NA	0 %
Lee et al. (2014)*	TSST	Self vs other social stress videos	40 (20)	African American (46 %)	34.72 (± 8.7)	NA	NA
Li et al. (2020)	Emotion Processing Task	Negative faces vs shapes	970 (508)	NA	28.69 (± 3.6)	14.95 (± 1.75)	NA
Ma et al. (2017)*	Shifted-Attention Emotion Appraisal Task	Implicit processing of emotional vs neutral faces	24 (12)	NA	22.8 (± 5.4)	NA	NA
Mercadillo et al. (2011)	IAPS Images Presentation	Social compassion vs social control scenes	39 (19)	Latin (100 %)	20.45 (± NA)	NA	0 %
Mercadillo et al. (2015)	IAPS Images Presentation	Social compassion vs social control scenes	96 (48)	Latin (100 %)	27 (± NA)	15 (± NA)	0 %
Merz et al. (2010)	Implicit Fear Conditioning Task	CS+ vs CS-	100 (49)	Caucasian (100 %)	23.2 (± 2.5)	NA	47.37 %
Merz et al. (2013)	Implicit Fear Conditioning Task	CS+ vs CS-	34 (17)	Caucasian (100 %)	23.22 (± 2.87)	NA	100 %
Min et al. (2023)	Emotion Regulation Task	“View” negative vs neutral images	40 (20)	NA	22.8 (± 2.64)	16.08 (± 2.09)	NA
Moriguchi et al. (2014)	IAPS Images Presentation	Negative vs neutral images	20 (10)	NA	43.05 (± 22.9)	NA	NA
Mueller et al. (2018)*	Cyberball Task	Social vs technical exclusion	80 (40)	Caucasian (100 %)	33.54 (± 10.54)	16.2 (± 2.38)	NA
Piefke et al. (2005)	Emotional Autobiographical Memory Presentation	Negative vs neutral memory script	42 (20)	NA	26.15 (± 2.25)	NA	NA
Radke et al. (2018)*	Cyberball task	Social vs technical exclusion	46 (24)	NA	24.54 (± 3.61)	NA	0 %
Repple et al. (2018)*	Modified Taylor Aggression Task	High vs low aggression provocation	92 (41)	NA	26.11 (± 6.05)	NA	NA
Sawyer et al. (2019)	IAPS Images Presentation	Aversive vs neutral images	28 (13)	NA	54.7 (± 13.9)	15.6 (± 2.25)	NA
Schienze et al. (2005)	IAPS Images Presentation	Fear vs neutral images	40 (20)	NA	28.57 (± 7.05)	NA	NA
Schneider et al. (2013)*	Empathy Task	Empathy-evoking vs neutral videos	96 (41)	Caucasian (100 %)	31.29 (± 13.24)	12.89 (± 0.32)	NA
Seifritz et al. (2003)*	International Affective Digitized Sounds System Sounds Presentation	Emotional vs neutral sounds	43 (23)	NA	30.95 (± 4.38)	NA	NA
Seo et al. (2011)	Autobiographical Memory Script Presentation	Stressful vs neutral memory scripts	1145 (458)	NA	27.09 (± 7.82)	15.08 (± 2.04)	0 %
Seo et al. (2017)	Autobiographical Memory Script Presentation	Stressful vs neutral memory scripts	30 (15)	Caucasian (51 %)	31.63 (± 9.28)	14.79 (± 1.97)	0 %
Spalek et al. (2015)	Picture Rating Task	Negative vs neutral images	74 (39)	NA	22.4 (± NA)	NA	57 %
Stark et al. (2006)	Fear Conditioning Task	CS+ vs CS-	100 (50)	Caucasian (100 %)	24.24 (± 7.5)	NA	100 %
Thomas et al. (2019)	IAPS Images Presentation	Negative vs neutral images	40 (20)	Caucasian (97 %)	25.2 (± 6.1)	14.9 (± 1.64)	NA
Veroude et al. (2013)	Emotional Stroop Task	Negative vs neutral words	51 (26)	NA	21.54 (± 0.58)	NA	NA
Wehrum et al. (2013)	IAPS Images Presentation	Negative vs neutral images	73 (37)	NA	25.5 (± 4.8)	NA	54 %
Williams et al. (2005)	Facial Expression Images Presentation	Fear vs neutral faces	119 (59)	Caucasian (100 %)	12.05 (± NA)	NA	NA
Zhang et al. (2022)	Chinese Affective Picture System Images Presentation	Sad vs neutral faces	34 (17)	Asian (100 %)	26.61 (± 1.87)	15.92 (± 0.74)	NA

Studies classified as ‘active’ are indicated with an asterisk (*), while the remaining studies belong to the ‘passive’ subgroup. Studies using non-exclusively negative stimuli are marked with a cross (×). Abbreviations: IAPS, International Affective Picture System; MIST, Montreal Imaging Stress Task; TSST, Trier Social Stress Task; SD, standard deviation.

2.5. Heterogeneity and publication bias

The heterogeneity of findings across studies was assessed using the I^2 statistic. To evaluate potential publication bias, an analogue to the Egger's test was applied, performing a meta-regression based on the standard error with a significance threshold of $p < 0.05$.

3. Results

3.1. Included studies and sample characteristics

We contacted the authors of all screened studies to retrieve

information regarding the sociodemographic variables of interest and/or statistical maps or double-check for possible inclusion. After screening all this information, sixty-three studies were included for the meta-analysis, producing sixty-three separate datasets for statistical analyses based on data from original publications and author responses. The total combined sample was made up of 5,436 individuals from the general population, from which 2,635 (48.47 %) were females. Twenty-six studies included (or provided) information on the race of participants for the subgroup meta-analyses. Sixty-two studies reported mean age, twenty-one studies reported years of education, and twenty-four studies reported the percentage of female participants who used contraceptives. Table 1 offers a comprehensive summary of the features of the datasets

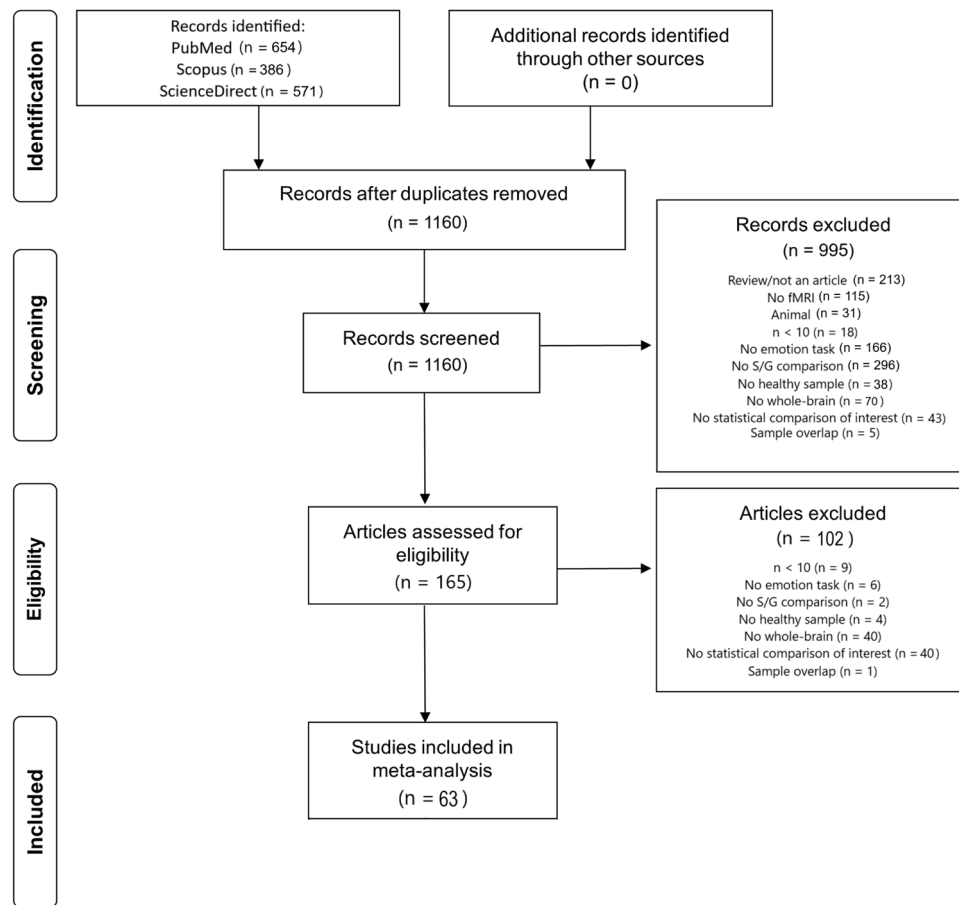


Fig. 1. PRISMA flow diagram illustrating the selection process for studies included in the meta-analysis (<https://www.prismastatement.org/>). Abbreviation: PRISMA, Preferred reporting items for systematic reviews and meta-analyses.

that were included.

The total mean age of participants was 28.64 years ($SD = 5.85$), with an age range spanning from 11 to 60 years old. The mean years of education was 15.06 years ($SD = 1.91$), ranging from 12 to 16 years. For the studies where the information was available, the mean proportion of female participants using hormonal contraceptives was 35 % (ranging from 0 to 100 %). Regarding task characteristics of the included studies, 57 employed visual stimuli (e.g., emotional vs. neutral images), three used auditory stimuli (e.g., emotional vs. neutral words), three applied sensory stimuli (e.g., painful stimulation), and one focused on olfactory stimuli (e.g., negative vs. neutral odours) (see Table 1 and Supplementary Table 1 for further information regarding the task and fMRI sequence used for each study).

3.2. Neuroimaging results

3.2.1. Main meta-analysis

The main meta-analysis did not reveal statistically significant S/G activation differences at the whole-brain level across all datasets, neither at the TFCE-corrected threshold ($p < 0.05$) nor at a more lenient uncorrected threshold ($p < 0.005$). The sensitivity analysis excluding studies using non-negative stimuli (11 studies) also indicated no statistically significant effects.

3.2.2. Subgroup meta-analysis by type of task

The subgroup meta-analysis for passive studies (52 studies) also showed no statistically significant results emerging for the contrast of interest at any threshold, neither when including all studies nor when performing the sensitivity analysis.

On the other hand, for the active subgroup meta-analysis (11 studies), three brain regions emerged showing statistically significant effects at TFCE- $p < 0.05$. Specifically, males showed higher activation than females during social evaluative stress (vs control) conditions in the opercular part of the right inferior frontal gyrus (IFG), the supplementary motor area (SMA), and the right insula (Table 2, Fig. 2). Of these, only the cluster in the right IFG survived Bonferroni correction (TFCE- $p < 0.007$).

3.2.3. Subgroup meta-analysis by race

The Caucasian subgroup meta-analysis (15 studies) did not show statistically significant results for the contrast of interest. On the other hand, in the subgroup composed of participants of other races (8 studies with primarily Asian samples, two studies with Latin samples and one study with a predominantly African-American sample), four clusters

Table 2

Results of the active subgroup meta-analysis (males > females).

Region	MNI coordinates (x, y, z)	Ke	SDM-Z	TFCE-p	I ²	Bias test (p-value)
Right IFG, Opercular*	54, 14, 30	169	-6.015	0.002	0.61	0.909
SMA	0, 2, 56	174	-4.919	0.015	1.22	0.603
Right insula	32, 24, 6	29	-5.078	0.035	2.16	0.606

* Results surviving Bonferroni correction (TFCE- $p < 0.007$). Abbreviations: MNI, Montreal Neurological Institute; Ke, cluster extent; SDM, Signed Differential Mapping; TFCE, Threshold Free Cluster Enhancement; I², percentage of variability associated with heterogeneity among studies; IFG, inferior frontal gyrus; SMA; supplementary motor area.

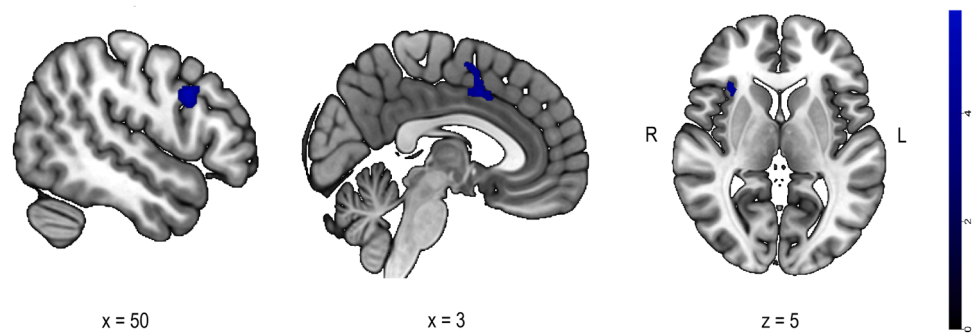


Fig. 2. Brain regions showing S/G differences (males > females) in activation for the contrast of interest in the active subgroup meta-analysis.

Table 3
Results of the other races subgroup meta-analysis (males > females).

Region	MNI coordinates (x, y, z)	Ke	SDM-Z	TFCE-p	I ²	Bias test (p-value)
Right SPL*	24, -72, 54	393	-4.062	0.005	2.42	0.812
Left lingual gyrus*	-14, -94, -6	97	-4.459	0.006	1.18	0.889
Right insula	36, 22, 0	49	-4.596	0.012	2.01	0.975
Left precuneus	-8, -72, 46	15	-3.847	0.035	1.05	0.810

* Results surviving Bonferroni correction (TFCE-*p* < 0.007). Abbreviations: MNI, Montreal Neurological Institute; Ke, cluster extent; SDM, Signed Differential Mapping; TFCE, Threshold Free Cluster Enhancement; I², percentage of variability associated with heterogeneity among studies; SPL, superior parietal lobule.

were identified in which females showed lower activation than males. These clusters were in the right superior parietal lobule (SPL), the left lingual gyrus, the right insula, and the precuneus (Table 3, Fig. 3). Of these, the clusters in the right SPL and the left lingual gyrus survived Bonferroni correction (TFCE-*p* < 0.007). In the exploratory subgroup analysis of predominantly Asian samples, a similar activation pattern emerged. Females again showed lower activation than males in the right insula (MNI = 42, 22, -6; Ke = 35330; SDM-Z = -5.33) and the precuneus (MNI = 8, -46, 12; Ke = 14; SDM-Z = -2.2). In addition, three new clusters emerged in this exploratory analysis, also showing lower activation in females: the left precentral gyrus (MNI = -28, -28, 54; Ke = 10; SDM-Z = -3.32); the left middle occipital gyrus (MOG; MNI = -42, -78, 14; Ke = 18; SDM-Z = -2.45), and the right hippocampus (MNI = 20, -34, 4; Ke = 10; SDM-Z = -2.24).

3.2.4. Meta-regressions

3.2.4.1. Age. No statistically significant associations were found between mean age and S/G activation differences at the selected threshold.

3.2.4.2. Education. Three clusters exhibited statistically significant positive associations between mean years of education and S/G activation differences. The first cluster was located in the left inferior occipital gyrus (IOG) and extended into the left fusiform gyrus. The second cluster was found in the hemispheric lobules IV/V of the right cerebellum, and the third was located in the left SPL (Table 4). None of these findings survived Bonferroni correction (TFCE-*p* < 0.007). As can be seen in their respective plots (see Fig. 4), at lower levels of education (around 12–14 years), females tend to show lower activation than males across these clusters. However, as education levels rise (around 15–16 years), this trend reverses, with females showing higher activation in these regions. Notably, despite these results being statistically significant, some studies across the full range of educational years (12–16) reported effect size values near zero, indicating minimal activation differences between males and females in these clusters for those studies.

3.2.4.3. Hormonal contraceptives. Eight clusters exhibited statistically significant associations with the proportion of females using hormonal contraceptives. The first two clusters survived Bonferroni correction (TFCE-*p* < 0.007) and were located in the dorsomedial prefrontal cortex (dmPFC), including the anterior cingulate cortex (ACC); and in the lobule VI of the right cerebellum, extending into the right lingual gyrus and the right fusiform gyrus. The remaining clusters were located in the cuneus, the vermis lobule VIII of the cerebellum, the right MOG, the left IFG (triangular part), the frontal pole, and the left amygdala (Table 4). A consistent pattern of findings is shown across these clusters: for those studies with no (or almost no) females using hormonal contraceptives, females displayed lower activation than males in these regions for the contrast of interest. This difference seems to diminish as the proportion of contraceptive use among females increases to 40–60 %, with effect size values approaching zero. Finally, for those studies with all females using contraceptives, females display higher activation than males in these clusters (see Fig. 5).

3.2.5. Heterogeneity and publication bias

Meta-analytic results mostly showed reduced heterogeneity according to the I² statistic, being the highest heterogeneity 26.31 %, while

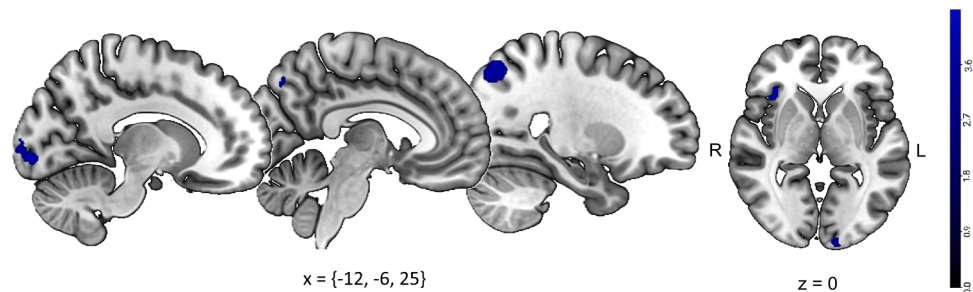


Fig. 3. Brain regions showing S/G differences (males > females) in activation for the contrast of interest in the other races subgroup meta-analysis.

Table 4
Results of the meta-regressions for education and hormonal contraceptives.

Meta-regression	Region	MNI coordinates (x, y, z)	Ke	SDM-Z	TFCE-p	I ²	Bias test (p-value)
Education	Left IOG	-34, -70, -8	299	2.985	0.016	6.04	0.639
	Right Cerebellum Lobes IV/V	8, -50, -16	45	2.870	0.038	5.78	0.606
	Left SPL	-26, -58, 46	39	2.593	0.046	21.28	0.694
Hormonal contraceptives	dmPFC*	0, 44, 28	1399	3.725	<0.001	1.16	0.990
	Right Cerebellum Lobule VI*	26, -76, -20	1305	3.045	0.003	0.44	0.992
	Cuneus	-4, -88, 24	421	2.154	0.023	0.1	0.994
	Cerebellum Vermis' Lobule VIII	4, -60, -30	233	2.642	0.015	0.77	0.993
	Right MOG	34, -86, 18	151	2.531	0.024	26.31	0.995
	Left IFG, Triangular	-52, 24, 6	97	3.071	0.014	7.15	0.992
	Frontal pole	14, 66, 6	73	2.267	0.041	1.85	0.994
	Left amygdala	-20, 2, -16	17	2.698	0.046	0.1	0.992

* Results surviving Bonferroni correction (TFCE-*p* < 0.007). Abbreviations: MNI, Montreal Neurological Institute; Ke, cluster extent; SDM, Signed Differential Mapping; TFCE, Threshold Free Cluster Enhancement; I², percentage of variability associated with heterogeneity among studies; IOG, inferior occipital gyrus; SPL, superior parietal lobule; dmPFC, dorsomedial prefrontal cortex; MOG, middle occipital gyrus; IFG, inferior frontal gyrus.

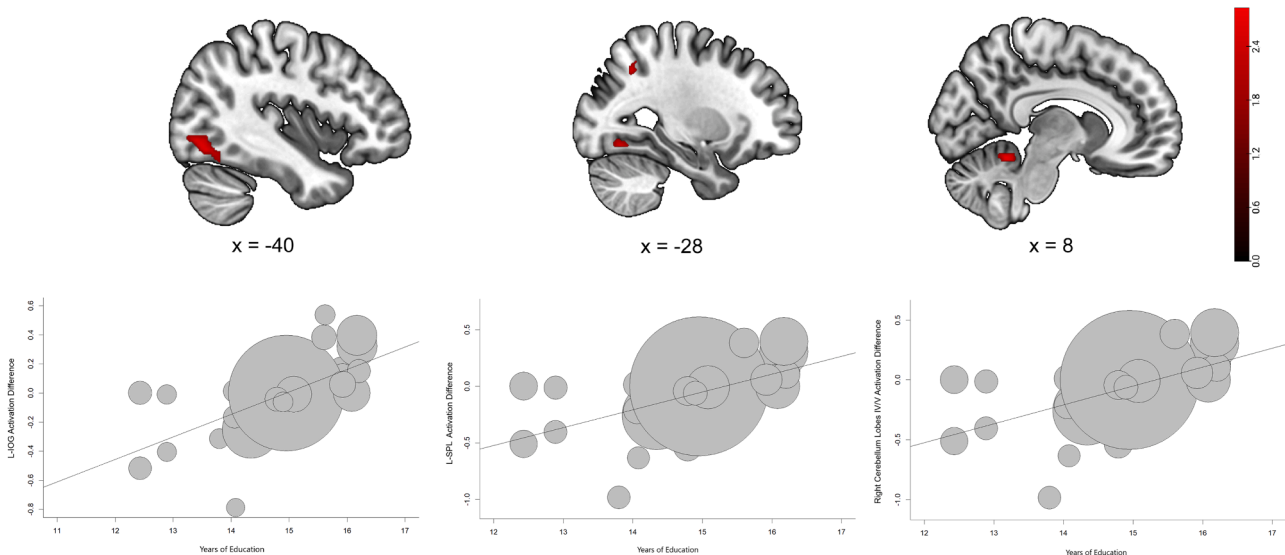


Fig. 4. Brain regions showing a positive correlation between mean years of education and S/G differences in activation for the contrast of interest. Positive values indicate greater activation in females relative to males. Abbreviations: IOG, inferior occipital gyrus; SPL, superior parietal lobule.

values above 50 % are considered to be an indication of severe heterogeneity (Ioannidis et al., 2007). Moreover, the results also presented a low risk of potential publication bias (a significant result would indicate publication bias; all *p*-values > 0.05, minimum *p*-value = 0.603), with no significant results for any brain region in the bias test (see also their corresponding funnel plots in Supplementary Figs. 1-4).

4. Discussion

The study of S/G differences in neuroscience grapples with methodological inconsistencies. Many studies continue to include exploratory analyses of S/G differences even when they are not initially meant (and designed) to expressly address them, further producing biased results which are rarely replicated, adding little to the literature of S/G effects on mental health and the brain (Bluhm, 2013; Bryant, 2019). Another prevalent issue is the lack of advancement in understanding how other factors influence brain function in interaction with S/G, highlighting the need for intersectional approaches (Subramaniapillai et al., 2024). Instead of pursuing more complex models of S/G effects, most research still focuses on S/G differences in brain structure or function during different processes from a rigid binary and essentialist perspective (Bryant, 2019; Helpman, 2023), and results are usually interpreted without considering other possible contributing factors (Rippon et al., 2017).

Our study attempts to partially address this gap, aiming to clarify this complex topic. The main meta-analysis did not yield statistically significant evidence of S/G differences during emotionally evocative conditions compared to neutral/baseline conditions, aligning with our initial hypothesis. This result echoes prior literature that challenges the overgeneralization of the brain's sexual dimorphism, instead emphasizing the critical role of individual variability (Eliot et al., 2021). Importantly, these null findings may be at least partially attributable to the heterogeneity of task paradigms used across studies. To address this issue, we conducted sensitivity and subgroup analyses aimed at capturing part of the variability associated with task characteristics. The sensitivity analysis showed that, even when restricting the meta-analysis to studies exclusively using negative stimuli, the absence of statistically significant S/G differences persisted, further confirming our hypothesis. The same was observed in the subgroup meta-analysis including passive tasks (i.e., tasks involving the exposure to emotional stimuli without requiring active task performance). In contrast, statistically significant S/G differences emerged in the subgroup meta-analysis of active tasks (i.e., tasks requiring participants' active engagement under actual or perceived assessment), with males showing greater activation than females in the right IFG (result surviving Bonferroni correction). These findings highlight the importance of considering not only individual variability when interpreting S/G effects, but also methodological variations in task design. More broadly, they underscore the risks of

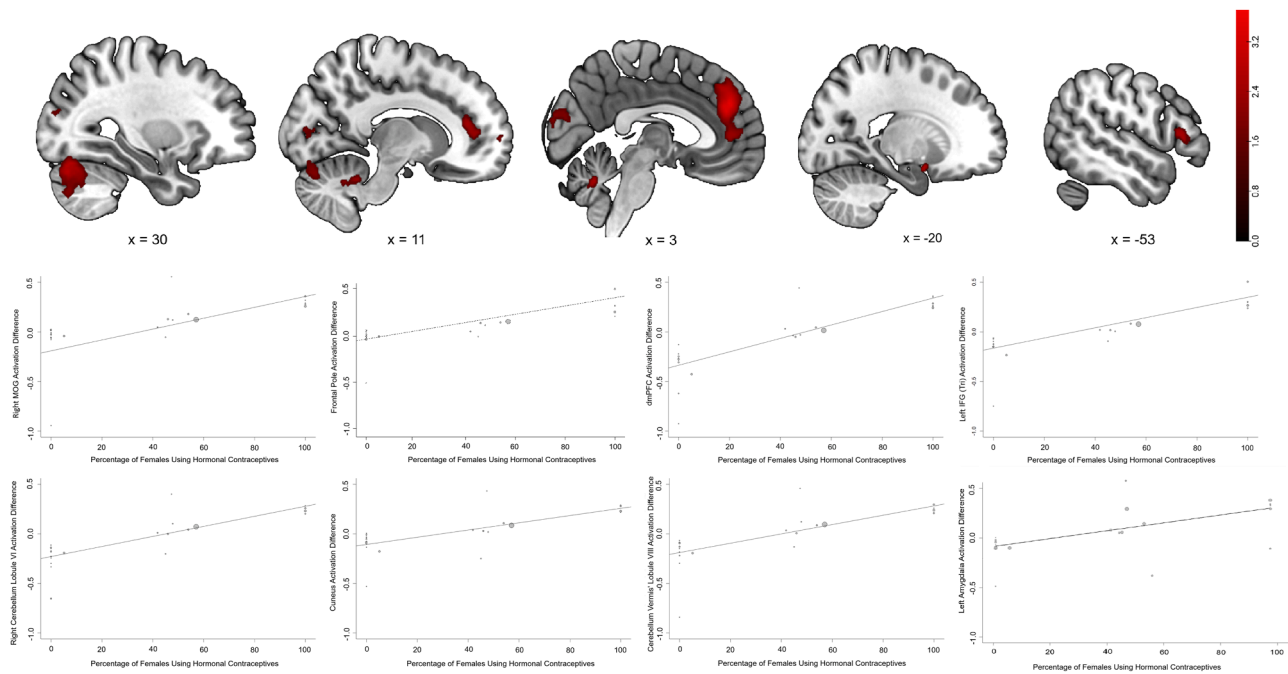


Fig. 5. Brain regions showing statistically significant associations between S/G activation differences and the proportion of females using hormonal contraceptives. Positive values indicate greater activation in females relative to males. Abbreviations: MOG, middle occipital gyrus; dmPFC, dorsomedial prefrontal cortex; IFG (Tri), inferior frontal gyrus, triangular part.

overgeneralizing S/G effects across contexts, and support social-contextual models over essentialist interpretations of S/G differences in neuroimaging research (Rippon et al., 2014).

Furthermore, we examined how other sociodemographic and biological factors influenced S/G differences in whole-brain activation for the contrast of interest. First, the subgroup analysis examining the influence of race on S/G whole-brain differences revealed statistically significant findings. Particularly, males from non-Caucasian racial groups showed significantly higher activation compared to females in several brain regions, including the right SPL and the left lingual gyrus (which survived Bonferroni correction), together with the right insula and the left precuneus. These regions have been linked to attention control during emotional processing and reappraisal, interoception and emotional awareness, as well as self-referential memory processing, respectively (Botta et al., 2021; Choi and Choi, 2024; Kogler et al., 2017; Oriolo et al., 2019; Ziv et al., 2013). These findings may result from factors such as different socialization and emotional expression norms, or task-specific strategies, influenced by current or past experiences based on cultural backgrounds (Lim, 2016). Our results may thus reflect an interaction between S/G and cultural effects, particularly through gendered socialization (Chaplin, 2015). Importantly, the non-Caucasian sample primarily consisted of Asian participants from studies conducted in Asian countries, which could impact the results due to cultural differences in emotional expression. Previous research has shown that people from collectivistic cultures, like many Asian groups, tend to suppress emotional expression more than those from individualistic cultures (Ford and Mauss, 2015). This cultural tendency may affect how emotional stimuli are processed in lab environments, resulting in variations in neural activation patterns.

It is important to note that these findings do not account for complex variables such as generational status (i.e., first-, second-, or third-generation of migrant families) or sociocultural distinctions depending on migration status within the same racial group, and how these differences interact with S/G. For instance, literature on racial discrimination (Brownlow et al., 2019) highlights differences in its nature depending on S/G: gendered racial discrimination, which remains unexplored here. This consideration is particularly relevant given that

most studies included in the analysis were conducted in predominantly Caucasian, normative contexts; and the non-Caucasian were performed mostly in Asian contexts, with Asian native participants. Either way, these results further emphasize the importance of including race as a key factor in future research to examine how sociocultural environments shape emotional processing, and their interaction with S/G.

Next, the meta-regression with education revealed S/G-specific activation patterns in the left IOG and SPL, and the right cerebellum. The observed differences indicate higher activation in males compared to females for lower years of education, in regions involved in visuospatial processing, memory and attentional control (Anderkova et al., 2018; Gil-Paterna & Furmark, 2023; Seo et al., 2017; Wong & Yu, 2024), with this pattern reversing as education levels increase. If interpreted as a whole, these results could indicate a differential reliance on self-related memory and attentional control switch during emotional processing, influenced by education. Caution is necessary when interpreting these results, given the small range of education years and the limited number of studies that reported education years in this analysis. However, these findings may reflect how environments associated with higher educational levels could differently influence males and females during emotionally aversive situations. Previous studies have shown that the impact of education on structural brain measures in older adults is influenced by demographic factors such as age and S/G, particularly in regions like the SPL (Bloomberg et al., 2021; Kang et al., 2021). However, it remains essential to understand how various factors interact to influence these patterns. For example, the interplay of specific environments and socially constructed S/G norms could influence these results by determining which populations have access to higher education and, therefore, its effects. Educational resources could, in turn, either reinforce or challenge gender norms, such as the expectation for individuals to either pursue higher education or remain at home or work in low-income jobs, which is strongly influenced by S/G (Picatoste et al., 2023; Rotman and Mandel, 2023). Since most of the samples included in the studies were university students or individuals with high levels of education, these results may reflect a complex interaction of these factors and lack, at the same time, heterogeneity to fully comprehend the influence of all levels of education on S/G differences. Therefore, it is

important to be cautious when interpreting these findings.

Regarding the hormonal contraceptive meta-regression, the brain regions that emerged as significant (highlighting the dmPFC and the right cerebellum lobule VI, which survived Bonferroni correction) have been previously associated with emotional processing, awareness, and reappraisal (Choi and Choi, 2024; Chin and Augustine, 2023; Dotson et al., 2022; Fonzo et al., 2017; Holtz et al., 2012; Huggins et al., 2024; Kim et al., 2023). Regarding the pattern of differences, with females showing higher activation in these regions compared to males as the percentage of females using hormonal contraceptives increases, previous literature has highlighted the impact of contraceptive use on mental health and brain changes associated with mood regulation (Concas et al., 2022). It has been proposed that, although the effect of hormonal contraceptives on emotion regulation remains inconsistent, their use could be linked to differential selection of emotion regulation strategies (Doornweerd et al., 2024). While the tasks included in this meta-analysis are designed to provoke emotions, unconscious emotion regulation is likely at play. Therefore, these results could reflect a tendency for differential automatic emotion regulation processes during these tasks between males, females using oral contraceptives, and females not using oral contraceptives, although this remains speculative.

Finally, contrary to our hypothesis, the meta-regression with age did not yield any statistically significant effects at the selected threshold, indicating that the absence of S/G differences observed in the main meta-analysis is consistent across the age range represented in the data. It is important to note, however, that age was not evenly distributed across studies, with most samples consisting of young adults with mean ages approximately between 20 and 35 years. Consequently, we cannot rule out the possibility that age-related modulation of S/G effects may be present in underrepresented age groups, as well as in specific population subgroups according to other factors (e.g. with higher or lower levels of education).

This study is not without limitations. For instance, although we were able to explore the impact of a sex-related variable dimensionally using the percentage of females taking oral contraceptives, it would be valuable to investigate other dimensional variables related to sex and gender, such as menstrual cycle phase, or gender roles, identity, or expression, to gain a broader understanding of these factors. In this line, it would also be of interest to explore other factors such as socioeconomic status or stress exposure. Regrettably, the studies included in the meta-analyses reported no (or very limited) information on these factors, limiting our subgroup and meta-regression analyses to those variables from which we were able to retrieve sufficient information. Future research including these additional dimensional variables is needed to provide a more comprehensive understanding of S/G-related effects. Also, the non-Caucasian subgroup lacked sufficient diversity, which may have impacted the generalizability of our findings in relation to race. Furthermore, while we attempted to implement an intersectional approach, in this study we only intersected S/G with each of the other variables individually, whereas we know that social reality is much more complex, with all variables interacting simultaneously. Moreover, while S/G differences were estimated within each primary study through within-study contrasts between females and males, socio-demographic information was only available at the study level (as means or proportion of participants from different groups), making these variables operate at different levels of analysis. Due to the limitations of the available data, more complex models that could account for these interactions were not possible, and as such, this study represents a first approximation to this topic.

In conclusion, our results go beyond traditional S/G comparisons, showcasing the need to account for how these factors interact dynamically to influence brain responses to emotionally salient stimuli. Crucially, our findings provide valuable insights into the complex interplay of S/G and other related variables in influencing S/G whole-brain differences during emotion-evoking fMRI tasks. By highlighting statistically significant patterns through sub-group and meta-regression

analyses, our study adds to the growing body of literature calling for a more nuanced understanding of S/G effects in the brain and mental health. These results serve as a stepping stone for the development of more complex models that integrate biological, psychological, and social dimensions. By doing so, future studies can yield deeper insights and pave the way for more sophisticated frameworks to understand S/G-specific emotional and stress-related processes.

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Data availability statement

The data used for this meta-analysis is either publicly available in the corresponding publications, or has been privately shared by the original authors for the purpose of performing the meta-analysis. The output data generated during the current study is available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Paula Ariño-Braña: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rita Vieira:** Writing – review & editing, Methodology, Investigation, Data curation. **Carles Soriano-Mas:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Joaquim Radua:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization. **Maria Picó-Pérez:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2026.121777](https://doi.org/10.1016/j.neuroimage.2026.121777).

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