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Gender discrimination facilitates fMRI responses and connectivity to thermal pain

Ming Zhang[a,b], Yuqi Zhang[a,b], Yan Mu[a,b], Zhaoxing Wei[a,b], Yazhuo Kong[a,b,c,*]

[a] CAS Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences, 16 Lincui Road, Chaoyang District, Beijing 100101, China
[b] Department of Psychology, University of Chinese Academy of Sciences, Beijing 100049, China
[c] Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford OX3 9DU, United Kingdom

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ABSTRACT

Gender discrimination is a serious social issue that has been shown to increase negative consequences, especially in females when accompanied by acute or chronic pain. Experiencing social pain through discrimination can increase an individual's evaluation of evoked physical pain. However, few studies have explored the mechanism underlying how gender discrimination modulates brain responses when individuals experience physical pain evoked by noxious stimuli. In this study, we addressed this issue using a gender discrimination fMRI paradigm with thermal pain stimulation. We found that discrimination indeed affected participants' own behavioral self-evaluation of noxious stimuli. Discrimination-encoded brain activations were identified in the temporopolar cortex, while brain activations to thermal stimuli after viewing pictures of discrimination were found in the dorsal anterior cingulate cortex (dACC). Brain activations in the temporopolar cortex and the dACC were correlated. Furthermore, pain perception-specific functional connectivity of the dACC-SII in the cue stage and the dACC-frontal in the pain stage were identified, suggesting a facilitative effect of gender discrimination on females' experience of physical pain. Our results indicate that the dACC may play a central role in mediating the affective aspect of physical pain after experiencing discrimination. These findings provide novel insights into the underlying mechanism of how gender discrimination facilitates females' experience of physical pain.

1. Introduction

Discrimination reflects a negative attitude and potentially unfair treatment toward people who have devalued identities (Pascoe and Smart, 2009). In response to the experiences of unfair treatment, discrimination-related information tends to arouse individuals' negative psychological states (Sullivan and Robinson, 2006). Discrimination has been linked to social pain, while it has been shown that individuals suffering prejudice struggle more with pain (Brown et al., 2018).

Just as physical pain has negative consequences (e.g., unpleasant and uncomfortable feelings), social pain from negative interpersonal interactions causes negative effects in individuals (Karos et al., 2018; Murphy et al., 2015). Furthermore, social pain and physical pain affect each other in terms of one's perception of both (Eisenberger, 2012; Zhang et al., 2019b). Previous studies have shown that experiencing social pain may enhance individuals' perception of physical pain (Eisenberger et al., 2006). For instance, experiencing social exclusion can increase an individual's pain sensitivity to the nociceptive stimulation produced by a pressure algometer (Bernstein and Claypool, 2012). In addition, due to continued potentially unfair attitudes and treatment, it has been reported that negative distress from discrimination can result in chronic pain (Brown et al., 2018). Perceived discrimination has been indirectly related to the intensity of body pain (Dugan et al., 2017) and chronic psychological distress, such as anxiety (Bakhshaie et al., 2019) and depression (McClendon et al., 2020). Although discrimination is the primary source of social consequences for individuals who have a devalued identity (Baumeister and Leary, 1995), there has been little research on how discrimination directly affects the processing of physical pain. Understanding this issue is especially important for groups that hold a stigmatized identity, which exhibit greater sensitivity to noxious stimuli (Kröner-Herwig et al., 2012) or suffer chronic pain (De Ruddere and Craig, 2016), in addition to having to face the serious issues of discrimination in society.

Neuroimaging studies have shown that experiencing social pain can activate the areas in the brain that are related to the emotional components of physical pain (Koban et al., 2017; Onoda et al., 2009), such as the dorsal anterior cingulate cortex (dACC), putamen, insula, and dorsomedial thalamus (Panksepp, 2003), all of which have been associated with physical pain experience (Aziz et al., 2000; Hu and Iannetti, 2016; Mouraux and Iannetti, 2018), as well as the right ventral prefrontal cortex (rVPFC), which is involved in regulating painful and negative af-

* Corresponding author.
E-mail address: kongyz@psych.ac.cn (Y. Kong).

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fective experiences (Lieberman et al., 2004). The dACC, in particular, is implicated in emotion regulation (Zilverstand et al., 2017), which is critical in coping with social stressors (Kraaij and Garnefski, 2019), and is one of the key neural structures involved in social and physical pain processes (Wager et al., 2009, 2016). These phenomena suggest that discrimination may arouse an increased feeling of physical pain. Indeed, increased brain activity involving the regulation of painful experiences (e.g., PFC (Lieberman et al., 2004)) has been found when individuals have passively viewed stigmatizing stimuli, showing bias against the stigmatized cue (Krendl et al., 2012). An electrophysiological study provided preliminary evidence for how social pain affected pain perception (using laser-evoked N1, P2 waves; Zhang et al., 2021). However, there is no direct evidence of how observed social pain (i.e., discrimination) affects brain responses to physical pain.

In the current study, we combined a discrimination-related fMRI paradigm (i.e., discrimination vs. control) with a thermal pain stimulation (i.e., low heat vs. high heat) to examine how discrimination-related images would modulate brain activity in pain-related areas when an individual experienced physical pain. We hypothesize that the pain-related region (e.g., the dACC), which is involved in higher-level cognition, would reflect the modulation of thermal pain by the discriminatory pictures. That is, that females would show an increase in brain response and connectivity in pain-related regions after viewing the discriminatory pictures, especially when high-intensity thermal pain was experienced. Our findings shed light on the psychological and neurological mechanisms underlying the effect of perceived discrimination on pain evaluation.

2. Materials and methods

2.1. Participants

Priori power analysis using G*Power Version 3.1 demonstrated that a sample size of 34 would allow for the detection of effect size ($f = 0.25$) with 80% power at an alpha of 0.05 for the repeated measures with two within-participant factors (i.e., discrimination vs. control, low heat vs. high heat), according to the criterion proposed by Cohen (1988) to test the medium effect (Faul et al., 2007). Thirty-four right-handed healthy female participants were recruited, while one participant was excluded from the study for failure to evoke pain perception based on the current stimuli intensities. In the end, a total of 33 participants (age = 22.21 ± 3.30 years, range = 18–30 years) took part in the current study, with 0.79 power to detect the estimated effect. The participants were instructed not to ingest pain medicine or alcohol for four hours before participating in the experiment (Kanarek and Carrington, 2004; Mercer and Holder, 1997). The experimental procedures were approved by the Institutional Review Board of the Institute of Psychology at the Chinese Academy of Sciences (No. H19046), and were performed following the Helsinki Declaration. All the participants were provided complete information regarding the study, were fully debriefed afterwards, and received RMB 150 as compensation for participating in the study.

2.2. Visual stimuli

The visual stimuli that served as conditional cues, which comprised 30 pictures that showed discrimination and 30 control pictures, were adopted from a previous study (Zhang et al., 2021). In that study, a set of pictures of discrimination were assessed as to whether they indicated gender discrimination (see stimuli samples in Fig. 1B) that would arouse females' feelings of discrimination based on their gender. In the study, the discrimination pictures used words or figures to indicate the devaluation of females, while the control pictures included no content relating to gender. The images were assessed by 30 female participants using two questions: (1) How likely do you think it is that the content in the picture reflected an issue concerning gender discrimination or sexism? (2) Indicate how you evaluated it – that is, to what extent did the content in the picture seem to you pleasant or unpleasant? The participants rated their response using a slider from 0 to 100% in increments of 10%. The top 30 discrimination pictures and 30 control pictures were selected for the materials, based on the rating rank and statistical test (Zhang et al., 2021). In the current study, the visual stimuli were presented via a video projector (frequency 60 Hz, resolution 1920 × 1080) onto a rear-projection screen mounted at the head of the scanner bore. The participants viewed the stimuli through a mirror on the head coil positioned over their eyes. All the stimuli (visual angle 11.18° × 7.74°) were displayed on a uniform black background.

2.3. Physical pain stimuli

Thermal stimuli were delivered using Pathway (Medoc, Compass Medical Technologies, Inc., North Carolina, USA), equipped with a fast-heating/fast-cooling probe with a 5.73 cm^2 surface area. In the scanner, the CHEPS (contact heat evoked potential) thermode was applied to the right forearm, 10 cm above the wrist. A four-second interstimulus interval and a 40 °C/second rate of temperature rise from a baseline temperature of 32 °C were used. The participants were asked to report their subjective evoked pain perception using a numerical rating scale (NRS) that ranged from 0 (no pain) to 10 (unbearable pain). Thermal temporal summation was measured by the participants' responses to 60 heat pulses with fixed temperatures of 42/45 °C, the two intensities perceived as being painful in the previous study (Loggia et al., 2011).

2.4. Procedure

Behavioral response collection was controlled by E-Prime 2.0 (Psychological Software Tools, Inc., Pittsburgh, PA, USA). Following the same procedure as the experiment, the participants performed a practice outside the MRI. Once inside the scanner, three sessions were conducted in total, each lasting 8 min. Each session included 20 trials with conditions (i.e., discrimination vs. control) and fixed-pain intensities (i.e., low heat 42 °C vs. high heat 45 °C) combined. The trial sequence in each session was pseudo-randomized with a trial time of 30 s. Each trial proceeded as follows (see Fig. 1A): First, a white fixation cross was presented for 0.9 s; then, one of the two conditional cues (i.e., discrimination or control) was presented for 4 s. Subsequently, a white fixation cross was presented for 0.1 s while, simultaneously, a heat pulse (42 °C or 45 °C) was delivered to the right forearm, which lasted for 4 s. A white fixation cross was then presented for 6 s. Thereafter, the participants were asked to consider the pain they had just felt and to provide pain ratings for the brief thermal stimuli using the NRS (displayed for 5 s) on a response box using their left hand. Finally, a black background screen appeared for 10 s before the next trial began. This process was repeated for a total of 60 trials.

Finally, having exited the scanner, the participants were asked to rate each stimulus picture used in the experiment to evaluate the images' degree of manipulation using two questions: (1) How likely do you think it is that the content in the picture reflected an issue concerning gender discrimination or sexism? (2) Indicate how you evaluated it – that is, to what extent did the content in the picture seem to you pleasant or unpleasant? The responses were conveyed by a slider that ranged from 0 to 100% to evaluate the level of the manipulation.

2.5. Data acquisition

A Siemens 3.0 T scanner (MAGNETOM Prisma, Siemens Healthcare GmbH, Germany) with a 64-channel head matrix coil was used for functional brain imaging. A participant's head was securely but comfortably stabilized with firm foam padding. Scan sessions began with transversal localization and sequential multi-slice mode. Functional data were acquired through an echo-planar imaging (EPI) sequence using a transversal orientation (46 slices, TR/TE = 1500/30 ms, slice thickness = 3 mm, FOV = 192 mm, matrix size: 94 × 94, in-plane resolu-

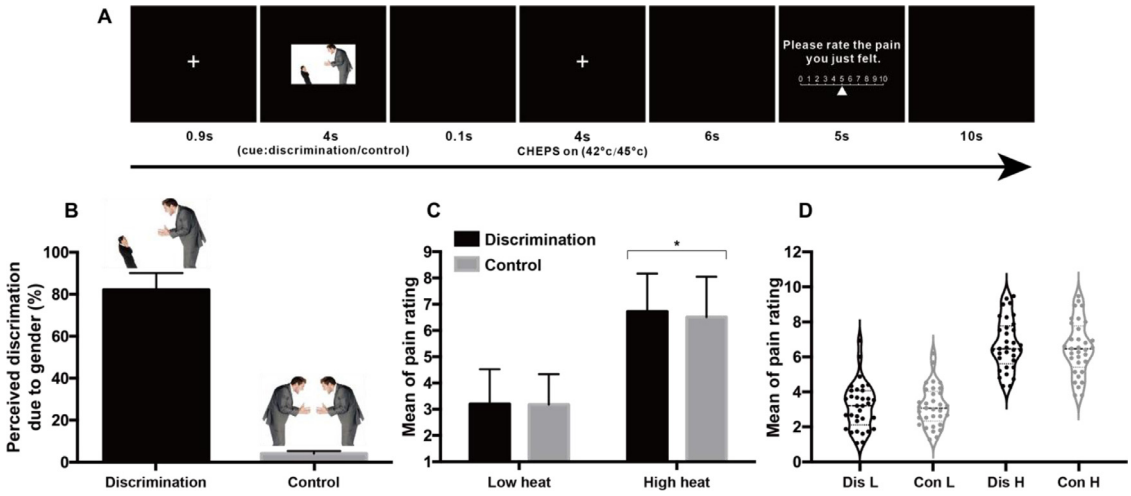

Fig. 1. Experimental design and behavioral results. (A) The experimental setup. (B) The material samples and the post-experiment simulation assessment. (C) The effect of condition on ratings of pain intensity (Error bars represent standard deviation, $p < 0.05$). (D) The violin plots for pain rating in the four combined conditions (i.e., Dis = discrimination, Con = control, *L* = low heat, and *H* = high heat).

tion = 2 × 2 mm^2, MultiBand = 2, GRAPPA = 2) covering the whole brain. A high-resolution T1-weighted 3D MPRAGE structural image was acquired between the first and second sessions of fMRI (transversal orientation, 192 slices, TR/TE = 1900/3.97 ms, FOV = 192 mm, resolution = 1 × 1 × 1 mm^3). The fieldmap was acquired between the second and third sessions of fMRI (transversal orientation, 49 slices, TR/ΔTE = 248/2.46 ms, FOV = 192 mm, resolution = 2 × 2 × 2 mm^3).

2.6. Data analysis

For behavioral data, the independent sample *T*-test was conducted to examine how the manipulation worked. Pain ratings were analyzed using a two-way repeated analysis of variance (ANOVAs), with cues and the intensity of thermal stimuli as the within-participant variables. fMRI data processing was performed using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). On the individual level, the following pre-processing steps were applied: motion correction using MCFLIRT (Jenkinson et al., 2002), non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 5 mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and high-pass temporal filtering. Registration from functional image to high resolution structural was performed using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002). Registration from high-resolution structural to standard space was then further refined using FNIRT nonlinear registration (Andersson et al., 2007a, 2007b). Each session of fMRI data was modeled on a voxel-by-voxel basis through a general linear model (GLM) approach (Woolrich et al., 2001), while parameter estimates (PE) were obtained for discrimination or control in the cue stages, and following low/high heat stimuli. A second-level analysis of the fixed-effects model was performed using within-subject activations across three sessions. Finally, a group level analysis was performed using a mixed-effects approach (FLAME, FMRIB's Local Analysis of Mixed Effects; Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004), while *Z* (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p = 0.05$ (Worsley, 2001). The repeated-measure analysis of variance and the independent sample *T*-test were performed across the subjects to investigate the brain regions involved in the variability of responses at low heat or high heat under discrimination or control conditions (i.e., discrimination-low, discrimination-high, control-low, and control-high).

Brain regions with significant activation differences in contrast (i.e., discrimination-high > control-high, that is, the discrimination condition in contrast to the control condition at high heat) were taken further to the region-of-interest (ROI) analysis (Cozzolino et al., 2019). Masks of ROIs were created in FSLeyes (part of FSL tools, http://fsl.fmrib.ox.ac.uk/fsl/fsleyes/) and further thresholded by Harvard-Oxford cortical and subcortical atlases. ROI masks were warped back to individual fMRI space. Average PE values within ROIs were extracted for each subject to explore their correlation with the subjective pain ratings given in the task in the scanner, or with the discrimination scores of figures given outside the scanner.

Furthermore, the psychophysiological interaction (PPI) analysis, with the dACC as the seed, was separately performed in the cue and the pain stages. We first extracted the mean timecourse from the dACC seed region using the preprocessed functional data. Next, the timecourse was added to the GLM at the individual level as the physiological regressor, with original task regressors as the psychological regressors. The final interaction (PPI) regressor is the scalar product of the psychological and physiological regressors. The individual parameter estimates for PPI were then taken to the normal higher-level group comparison (Methods 2.6). The demeaned pain rating, as an additional explanatory variable, was performed in the GLM at the group level to test whether there was pain perception-specific functional connectivity (PPI analysis in Feat, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PPIHowToRun).

3. Results

3.1. Post-experiment manipulation check

The *T*-test revealed that the participants reported more discrimination when they viewed the discrimination pictures (*Mean* ± *SD*, 81.31 ± 12.45) than when they viewed the control ones (2.91 ± 5.03), $t_{(64)} = 33.55$, $p < 0.001$, $d = 8.26$. Additionally, the participants reported feeling more unpleasant toward the discrimination pictures (79.56 ± 12.23) than toward the control pictures (11.30 ± 11.99), $t_{(64)} = 22.89$, $p < 0.001$, $d = 5.64$. Expectedly, the materials used for manipulation affected the participants' perception of gender discrimination and aroused their negative emotions.

3.2. Psychophysics

Two-way ANOVA revealed that both the main effects of the condition (i.e., discrimination vs. control) and intensity (i.e., low heat

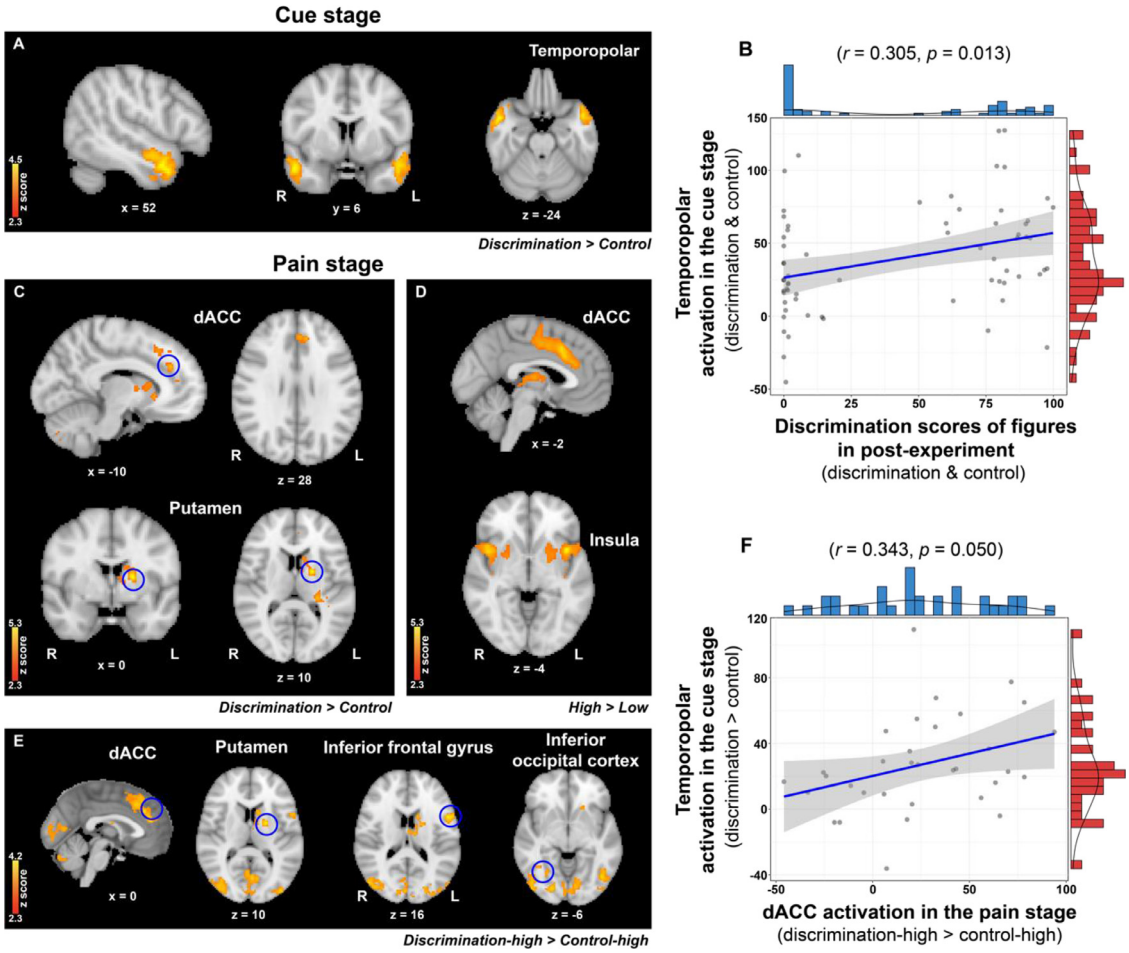

Fig. 2. Whole-brain analysis. (A) During the cue stage, brain activation of the temporopolar cortex was significantly increased in the discrimination condition compared to the control condition. (B) Correlation between temporopolar cortex activation (i.e., in both discrimination and control conditions, abbreviated as discrimination & control) and the discrimination scores of figures (discrimination & control). (C) Brain activation of the dACC and the putamen was significantly increased during the pain stage in the discrimination condition when compared to the control condition. (D) Brain activation of the dACC and the insular was significantly increased at the high heat level when compared to the low heat level. (E) Brain activation of the dACC, the putamen, the inferior frontal gyrus, and the inferior occipital cortex was significantly increased in the discrimination condition, compared to the control condition, at high heat ($p < 0.05$, cluster-corrected 2.3). (F) Participants' increased brain activation in the left temporopolar cortex (i.e., brain activation in the discrimination condition compared to that in the control condition, abbreviated as discrimination > control) was significantly positively correlated with brain activity in the dACC (i.e., brain activation in the discrimination condition compared to that in the control condition at high heat, abbreviated as discrimination-high > control-high).

vs. high heat) were significant: $F_{(1,32)} = 5.13$, $p = 0.03$, $\eta_p^2 = 0.138$; $F_{(1,32)} = 333.41$, $p < 0.001$, $\eta_p^2 = 0.912$. The interaction of condition and intensity also reached significance: $F_{(1,32)} = 5.41$, $p = 0.027$, $\eta_p^2 = 0.145$. A post hoc analysis showed that the pain rating in the discrimination condition (6.72 ± 1.45) was significantly higher than in the control condition (6.51 ± 1.54) at the high heat condition, $t_{(64)} = 3.01$, $p = 0.005$, $d = 0.14$ (Fig. 1C and D), indicating that the stronger thermal stimuli were more severely impacted by the discrimination manipulation.

3.3. fMRI results

Whole-brain analysis. In the cue stage, the analysis of the fMRI data revealed increased activity in the bilateral temporopolar area ([–48, 8, –26], [52, 6, –24]) in the discrimination condition, in contrast to the control condition (Fig. 2A). The temporopolar activation was significantly correlated with the participants' discrimination scores (Spearman correlation analysis, $r = 0.305$, $p = 0.013$, Fig. 2B). In the pain stage, the data revealed increased activity mainly in the dACC and the putamen in the discrimination condition, in contrast to the control condition (Fig. 2C). Similar responses were seen in the dACC and the bilateral insula in the high heat condition, in contrast to the low heat condition (Fig. 2D). Interestingly, increased activity in the dACC, the putamen, the inferior frontal gyrus, and the inferior occipital cortex was seen in the discrimination-high condition, in contrast to the control-high condition (Fig. 2E).

ROI analysis. We examined the increased activity in the pain-related neural regions in the discrimination condition relative to the control condition, particularly in the high heat condition. Specifically, we focused on the dACC and the putamen. Expectedly, the participants showed enhanced activity in the dACC ([0, 40, 22]) and the putamen ([–20, 0, 10]) in the discrimination condition, compared to the control condition, at both low heat and high heat ($t_{(64)} = 3.99$, $p < 0.001$, $d = 0.49$, Fig. 3A; $t_{(64)} = 6.44$, $p < 0.001$, $d = 0.83$, Fig. 3C). This reflects that the activation in the pain-related neural regions was more intense in the discrimination condition than in the control condition at any pain intensity level. Moreover, the changed pain perception in the discrimination condition, when compared to the control condition (i.e., the mean of behavioral pain ratings at both low heat and high heat in the discrimination condition, compared to that in the control condition), was marginally positively correlated with neural activity in the putamen ([–20, 0, 10], $r = 0.303$, $p = 0.087$, Fig. 3D; i.e., brain activation in the discrimination condition compared to that in the control condi-

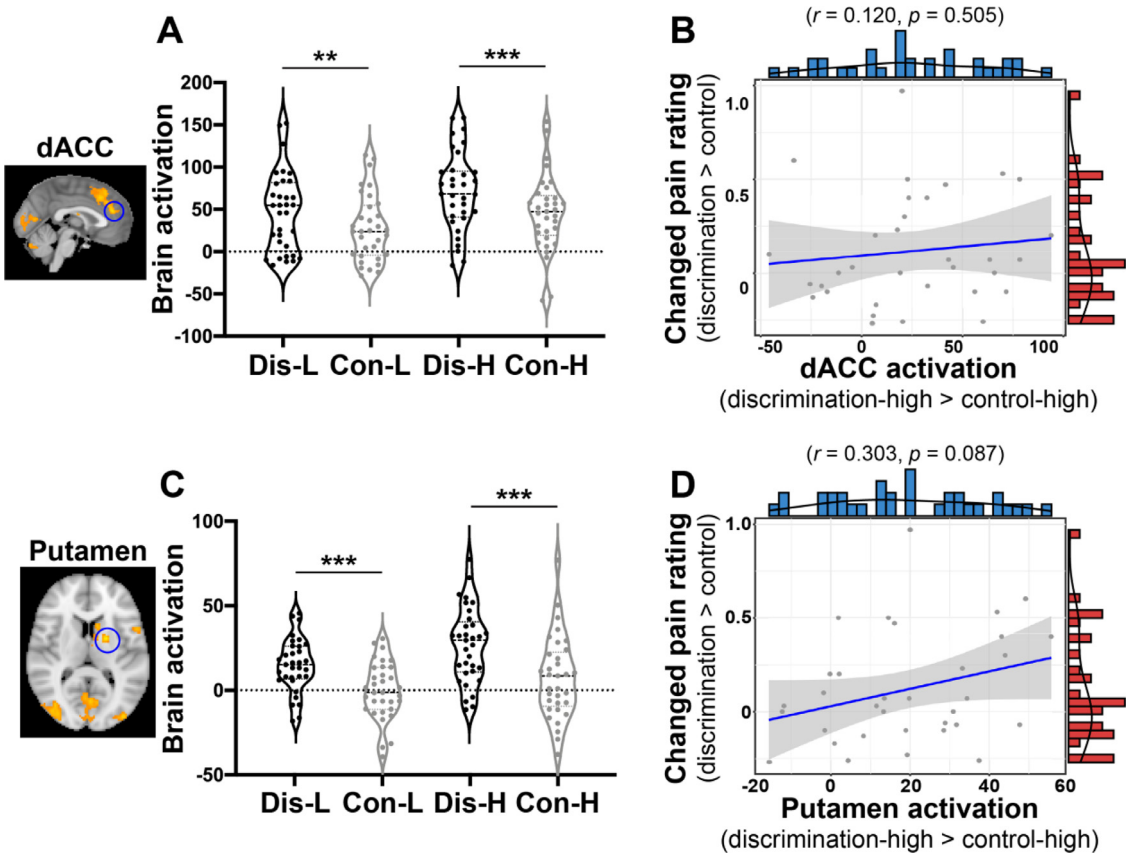

Fig. 3. ROI analysis. (A) ROI analysis revealed that brain activation of the dACC was significantly higher in the discrimination condition than in the control condition at two intensity levels (i.e., Dis = discrimination, Con = control, *L* = low heat, and *H* = high heat). (B) The scatter plot showing the correlation between brain activation in the dACC (i.e., brain activation in the discrimination condition compared to that in the control condition, at high heat, abbreviated as discrimination-high > control-high) and the changed pain rating (i.e., the mean of behavioral pain ratings at both low heat and high heat in the discrimination condition compared to that in the control condition, abbreviated as discrimination > control). (C) ROI analysis revealed that, at both intensity levels, activation of the putamen was significantly higher in the discrimination condition than in the control condition. (D) The scatter plot showing the correlation between brain activation in the putamen (discrimination-high > control-high) and the changed pain rating (discrimination > control).

tion at high heat). We did not find a significant correlation between the changed pain perception and brain activation in the dACC ([0, 40, 22]), $r = 0.120$, $p = 0.505$, Fig. 3B), although the measured correlation was positive.

To examine the effect of the cue stage on the pain stage, we calculated the correlation between the brain activation of the temporopolar cortex in the cue stage and the brain activation in the pain stage. The increased brain activity of the left temporopolar cortex in the discrimination condition, compared to that in the control condition (discrimination > control), was significantly positively correlated with increased brain activity in the dACC in the discrimination condition when compared to that in the control condition at high heat (discrimination-high > control-high), $r = 0.343$, $p = 0.050$ (Fig. 2F).

PPI analysis. We first compared the dACC-based PPIs in the discrimination and the control conditions in the cue stage and those in the pain stage. There was no significant difference in PPI in the discrimination condition compared to the control condition. However, different pain perception-specific (positively related to pain ratings) connectivity was found separately in both the cue and the pain stages. In the cue stage, significant pain perception-specific connectivity was identified between the dACC and the left secondary somatosensory (SII) cortex ([60, –26, 26]), as well as the right inferior temporal gyrus ([46, –62, –10], Fig. 4A), suggesting a modulation effect of sensory input before the thermal stimulation. Meanwhile, in the pain stage, significant pain perception-specific connectivity was identified between the dACC and the right superior temporal gyrus ([48, 5, –22]), as well as the frontal pole ([–2, 54, 22], Fig. 4B), suggesting a possible emotional regulation mechanism when receiving thermal pain with discrimination.

4. Discussion

The current study sought to understand how perceived gender discrimination impacted an individual's pain perception, as reflected by neural responses to noxious stimuli. By observing the participants' experiences of being discriminated against in ways that they may experience in the future (i.e., personally-relevant situations), we found that exposure to discrimination scenarios affected the participants' behavioral evaluations and brain responses to the noxious stimuli. First, our findings showed preliminary evidence that the neural mechanisms underlying such effects of discrimination were associated with the brain activity of the temporopolar cortex. Second, our results showed that the brain activation of the pain-related cortical areas (i.e., dACC and putamen) increased significantly in the discrimination condition compared to the control condition, and that the increased brain activation marginally correlated with the individual's perception of pain regarding the thermal stimulation. Third, activation of the temporopolar cortex during the discrimination cue correlated highly to increased dACC activity in the pain stage, suggesting that discrimination played a salient role in the perception of physical pain. Fourth, PPI analysis indicated that there was pain perception-specific dACC-SII connectivity in the cue stage and dACC-frontal connectivity in the pain stage. Overall, our findings confirm that experiencing gender discrimination increases physical

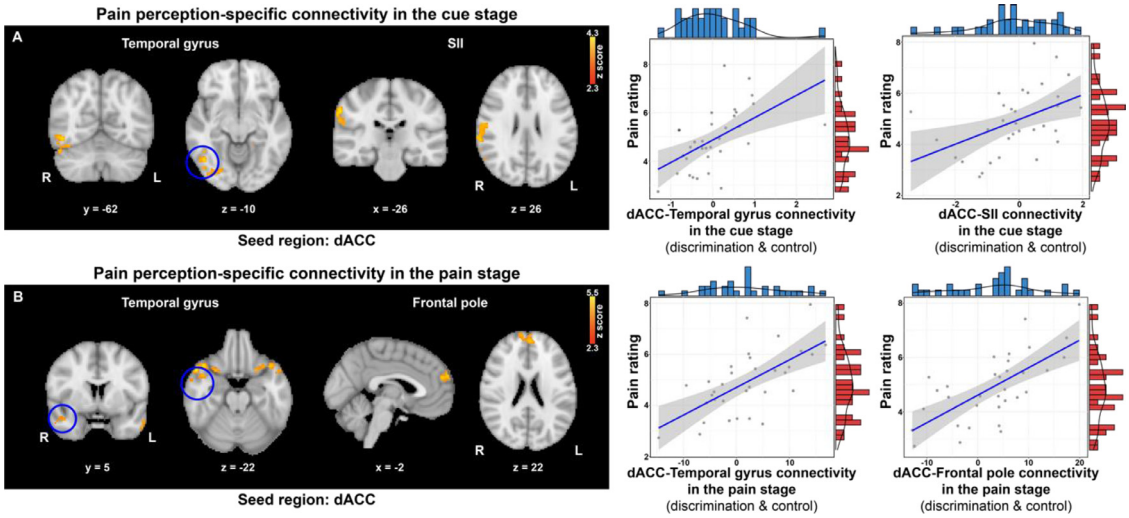

Fig. 4. PPI results. (A) Whole-brain functional connectivity analysis in the cue stage revealed pain perception-specific dACC-temporal gyrus and dACC-SII connectivity (i.e., connectivity in both discrimination and control conditions, abbreviated as discrimination & control; $p < 0.05$, cluster-corrected 2.3). (B) Whole-brain functional connectivity analysis in the pain stage revealed pain perception-specific dACC-temporal gyrus and dACC-frontal pole connectivity ($p < 0.05$, cluster-corrected 2.3).

pain evaluation, and further suggests that the temporopolar cortex and dACC may play key roles in the interaction between social pain and physical pain.

4.1. Temporopolar cortex encoded gender discrimination experience

In contrast to previous findings that have suggested that experiencing social rejection (e.g., from an ex-partner) activates the overlap regions between social rejection and physical pain (e.g., the secondary somatosensory cortex; Kross et al., 2011), the current study found increased activity in the temporopolar cortex in the discrimination condition when compared to the control condition in the cue stage, as well as temporopolar cortex activation that significantly correlated with the discrimination scores. The temporopolar cortex is already known to be associated with mind-wandering (Fox et al., 2015) and self-perspective (Vogeley et al., 2001). The temporopolar cortex also appears to play an essential role in social emotion processing (Tso et al., 2018), involved mentalizing (Olson et al., 2007), and personal autobiography (Bulbulia and Krueger, 2009). Since the temporopolar cortex has been implicated in mentalizing and autobiography, our results may reflect that the participants were thinking about the experience of the person being discriminated against when they viewed those cues that contained gender discrimination. Thus, such passive observation of gender discrimination may also have consequences similar to those of the experience of discrimination.

Social pain arouses various adverse effects (Auyeung and Alden, 2016). Gender discrimination is one of the social pains that heighten negative emotions in females and negatively impact behavior and perception (Kinkel-Ram et al., 2021; Zhang et al., 2019a, 2021). Sexism-related cues, such as information devaluing of females, can evoke feelings of potential threats (Logel et al., 2009) and negative interaction expectations (Zhang et al., 2019a). The participants in the current study did not actually experience gender discrimination as part of the experiment; yet, seeing stimuli that were merely suggestive of other females experiencing gender discrimination, which could hypothetically happen to the participants themselves at some point, still produced observable negative emotions. Moreover, the temporopolar cortex is particularly associated with self-related information (Chiao et al., 2012). The brain activity in the temporopolar cortex that was evoked by sexism-related stimuli (in the cue stage) implied a potential effect of gender discrimination on the subsequent pain perception of thermal stimuli (in the pain stage).

4.2. Discrimination-induced activation related to pain-sensitive brain responses

The current study found a positive correlation between brain activation of the temporopolar cortex in the cue stage and brain activation of the dACC in the pain stage. Our results showed that greater activation of the temporal cortex in the cue stage was accompanied by increased brain activation in the pain-sensitive regions (i.e., dACC) in the pain stage. The dACC plays an important role in higher-level functions, and is involved in the perception of both physical pain and social pain (Wager et al., 2016). Woo et al. (2014) identified distinct functional connectivity patterns within the dACC, and showed that stronger functional connectivity between the thalamus, posterior insula, medial frontal regions, and midbrain was found when the dACC engaged with physical pain, whereas when engaged with social rejection, the dACC was more strongly associated with the ventral and dorsal lateral prefrontal cortex, temporal pole, and parietal cortex. The potential connection between the dACC and temporal cortex while experiencing social pain may suggest that discrimination-related information directly influences the processing of pain perception in response to subsequent noxious stimuli.

4.3. dACC may play a central role in the facilitative aspect of the physical pain experience after discrimination

In behavioral performance, we observed that the pain rating in the discrimination condition was higher than that in the control condition, especially at the high-intensity noxious stimuli level. Discrimination-related stimuli containing potential threats have also shown a tendency to heighten negative emotions in females (Zhang et al., 2019a). Emotions can modulate pain encoding (Tseng et al., 2017), which indicates that a negative mood increases pain perception. Seemingly, the more pain the participants in the current study experienced, the stronger that pain was modulated by the negative stimuli.

Notably, the brain activity in the dACC and the putamen was significantly increased in the discrimination condition when compared to the control condition, suggesting that perceived gender discrimination enhanced brain activation of pain experienced from thermal stimuli. Our findings are consistent with those of previous studies that have shown that neural correlates of social pain are usually found to involve the putamen and the dACC (He et al., 2019; Wager et al., 2016). Activity in the dACC has previously been observed in individuals experiencing social exclusion (Onoda et al., 2010) or viewing rejection-related imagery

(Kross et al., 2007), especially during tasks requiring emotion regulation (Decety et al., 2010; Lin et al., 2018), which supports our findings that the dACC activation will also appear in response to a potentially negative effect arising from perceived gender discrimination. Particularly, the observed increased BOLD responses in the dACC at the high heat level indicated that gender discrimination had a greater effect on high heat perception. Compared to low heat, based on the stronger intensity and salience, high heat has been perceived as worse and more unpleasant (Gagnon-Dolbec et al., 2021; Oliva et al., 2020). Given that the negative emotion evoked by high-heat stimuli accompanied the negative effect from the previous sexism-related cue, neural activity in the dACC would overlay; thus, the negative effect on pain perception would be amplified. Therefore, the facilitating effect of discrimination on high heat was more obvious than on low heat. Moreover, brain activation and behavior changes under the different conditions were consistent at high heat, implying a potential connection between brain response and behavioral performance.

Furthermore, our results showed that pain perception-specific connectivity between the SII/temporal area and the dACC in the cue stage was associated with an individual's pain perception. This pre-stimulus pain perception-specific connectivity may remain vigilant for subsequent noxious stimuli. Correspondingly, the connectivity between the frontal pole/temporal area and the dACC, in the pain stage, was also significantly correlated with an individual's pain perception, suggesting a modulated effect on the reappraisal of pain-intensity perception. Briefly, it seems that the potential functional connection in the cue stage played alertness and anticipation; thus, the reappraisal of pain perception could work in the pain stage. These cortico-cortical interactions reflect the fact that the dACC-SII/temporal area connectivity was regulated when females viewed stimulus materials passively, while the dACC, as well as multiple other areas, was involved in pain enhancement in the subsequent pain stage.

5. Limitations

Although we believe that our results offer important evidence regarding the negative effect of gender discrimination on individuals' perception of pain, we acknowledge limitations in the present study.

First, we should note that the observed effect size of behavioral performance on high heat due to gender discrimination was not large in the present study, i.e., 0.21 points difference on an 11-point scale. The results were consistent with a previous study (Zhang et al., 2021), while we believed that a slight difference in reported pain might reflect a clear difference in psychological feelings (Halpern, 2015). Yet, it may be helpful to use large scales (e.g., 0–100 scale (Hosomi et al., 2020)) to measure pain perception, or to adopt a better discrimination-related task to enlarge the weak effect for future applications. Additionally, we conducted the manipulation check after the participants had completed all the tasks, which could elicit varying degrees of demand effects (Zizzo, 2010). Therefore, there is a risk of exaggerating the effect size. In other words, the demand effects induced by the order of the manipulation-check questions could explain the immense effect size. This limitation could be improved by pre-manipulation testing before the experiment, or by performing a timely figure rating before the pain-rating trial in future studies.

Second, the ROIs (dACC and putamen) were defined based on the results of the contrasts in the whole-brain analysis rather than adopting the locations from a particular previous study, despite these regions having been reported to be activated by noxious stimuli in many previous studies (Bingel et al., 2004; Wager et al., 2016). It would be more reliable and certain to verify a similar effect with these stimuli by examining the functions of the same regions as mapped out in similar previous studies.

Third, most participants in our sample were college students, meaning that they had not yet experienced years of gender discrimination in the workplace, which was the model for our discrimination condition. Indeed, gender discrimination may occur in broader contexts. However, it is noteworthy that we observed a salient effect when college-age participants observed others experiencing gender discrimination instead of experiencing it themselves, which implied a negative effect on individuals' daily lives.

Fourth, our study focused on the effect of gender discrimination on females. However, males must also face issues of discrimination, albeit in different circumstances, for example, in a career which is stereotypically female, such as in nursing (Kouta and Kaite, 2011). It would be helpful to conduct a comprehensive examination into the negative effect of gender discrimination as experienced by all genders, by testing in broad groups.

Conclusion

The current study investigated the neural mechanisms underlying the effect of gender discrimination on female pain perception. The findings show that the dACC is involved in the brain response to the effect of gender discrimination on pain perception, which is associated with the temporopolar cortex. To our knowledge, the current results provide the first evidence that watching or sharing others' feelings about being discriminated against (not simply directly experiencing discrimination) increases one's own physical pain experiences and evaluations, suggesting an overlap between sharing in others' discrimination experiences at a psychological level and feeling one's own pain perceptions at a physical level. Considering that discrimination-related social issues are experienced across a broad spectrum of society, and that addressing issues of discrimination is of high relevance in today's world, our research is of great representational significance concerning the more obscure impacts of discrimination against individuals. More importantly, our findings provide novel insight into how we might create interventions to reduce pain in future experiences of discrimination in the future. A simple example is to provide in-depth treatment and support for female patients with chronic pain, and to not assume that women overreact to diseases simply because they are women, which creates barriers to their access to more treatment opportunities.

Credit authorship contribution statement

Conceptualization: Ming Zhang, Yan Mu, and Yazhuo Kong; Data curation: Ming Zhang and Yazhuo Kong; Formal Analysis: Ming Zhang and Yazhuo Kong; Funding acquisition: Ming Zhang, Yan Mu, and Yazhuo Kong; Investigation: Ming Zhang, Yuqi Zhang, and Zhaoxing Wei; Methodology: Ming Zhang, Yan Mu, and Yazhuo Kong; Writing–Original Draft: Ming Zhang, Yan Mu, and Yazhuo Kong; Writing–Review and Editing: Ming Zhang, Yan Mu, and Yazhuo Kong.

Open science statement

We conducted exploratory research, which was not preregistered. The hypothesis and analyses were explicitly marked as exploratory. The study was planned in such a manner that the sample sizes allowed us to achieve sufficient statistical power, which was a-priori determined on the basis of power analyses. We support replication, and aim to make available non-successful replications of our own as well as others' findings.

Data and code availability statement

The behavioral data, the fMRI data, and the codes are available at: https://osf.io/snwxa/?view_only=62c0d28c539f4b15b1889edc93a0f690.

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