Should perception of emotions be classified according to threat detection rather than emotional valence? An updated meta-analysis whole-brain atlas of emotional faces processing

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ABSTRACT

Background: Human navigation of social interactions relies on the processing of emotion on faces. Previous theories of emotional processing on human faces were based on a mixture of studies of emotional experiences during observation of emotional scenes and perception of emotional faces, which have led to a variety of views. This meta-analysis aimed to produce an updated brain atlas of emotional face processing of whole-brain studies based on a single emotional face viewing paradigm and to contribute to the theorization of emotional face processing in human (PROSPERO CRD42022251548).

Methods: A systematic literature search using the databases EMBASE, MEDLINE, and APA PsycINFO took place from May 2008 to October 2021. Seed-based *d* mapping with permutation of subject images quantitatively voxel-based meta-analyzed functional neuroimaging contrasts between emotional (e.g., angry, happy) and neutral faces. Agglomerative hierarchical clustering of meta-analytic map contrasts of emotional relative to neutral faces examined the processing similarity across emotions. Lateralization of emotional face processing was examined in amygdala, anterior insula, and ventromedial prefrontal cortex (vmPFC) regions.

Results: From 5549 studies initially identified, 55 datasets (1489 healthy participants) met our inclusion criteria. Relative to neutral faces, we found extensive activation clusters by fearful faces in right inferior temporal gyrus (ITG), right fusiform area (FFA), left putamen/amygdala, right PHG, and cerebellum; and smaller activation clusters by angry faces in right cerebellum and right middle temporal gyrus (MTG); and by disgusted faces in left MTG. Happy and sad faces did not reach statistical significance. Clustering analyses showed similar activation patterns of fearful and angry faces, while activation patterns of happy and sad faces showed the least correlation with other emotional faces. Emotional face processing was predominantly left-lateralized in amygdala and anterior insula, and right-lateralized in vmPFC.

Conclusion: Processing of emotional faces in the human brain appeared to be oriented towards identifying threats on the faces, from the highest (i.e., angry or fearful faces) to the

lowest level (i.e., happy or sad faces), with a more complex lateralization pattern than previously theorized. Emotional faces may thus be processed in latent grouping but organized by threat content rather than emotional valence.

1. INTRODUCTION

Human beings are socially complex species[1]. Our ability to navigate social interactions is dependent, among others, on the effective processing of emotions on faces. Such processing allows us to recognize others' affective states and enables appropriate cognitive and behavioral adjustment during interpersonal exchanges[2]. The emotional face processing follows a slow developmental course, but the ability to detect facial emotion categories is present already in young infants[3, 4]. Discrete categories of facial emotions are also observed across cultures[5, 6] although there are cross-cultural differences in the categorization and interpretation of these emotions[7].

These observations lead to several theorizations of how emotion, in general, is processed in the brain. The classical *"locationist"* view of emotional perception assumes that there exists a set of discrete and universal emotional categories, and each emotional category is associated with distinctive neural signatures[5]. In contrast, the *"constructionist"* view proposes that all emotions are processed by a common underlying brain network, which becomes psychologically attributed to a different and discrete range of emotions based on prior experiences[8]. Others attempt to bridge these fundamentally opposing views by suggesting that the processing of emotions occurs, at least, in latent groupings, for instance, according to a broad valence polarity where negative emotions (i.e., fearful, anger, disgust and sadness) are processed distinctly from positive ones[9].

It is unclear which of these theories best described the brain processing of *emotional faces,* however, as most theorization were based on meta-analytic findings of brain activation during a variety of emotional processes (e.g., experiencing emotional scenes and perceiving emotions on faces). These potentially different processes might indeed rely on overlapping brain regions such as the limbic system and insular cortices[8, 10, 11]. However, each emotional face category might also engage specific cortical activation in visual, temporoparietal, prefrontal, including the inferior and orbitofrontal areas, and cerebellar cortices, as has been observed during the viewing of emotional relative to neutral faces[12-14].

Among the meta-analyses that have contrasted discrete emotion relative to neutral faces, some findings suggested commonality and specific brain activation across the emotional categories. In our previous meta-analysis involving overall 105 unique whole-brain and region-of-interest studies, amygdala activation was reported during the processing of happy, fearful and sad faces but not angry or disgusted faces, that selectively activated the insula[12]. A recent meta-analysis including overall 141 studies has found that left or bilateral amygdala activation was involved in the processing of happy, sad, angry and fearful, but not disgusted faces[15]. Angry faces, which activated the left pallidum and right fusiform face areas (FFA), right posterior middle temporal and occipital gyri; and fearful faces, which activated similar areas including bilateral pallidum, left IFG, left FFA, and bilateral occipital areas, appeared to activate more brain regions than any other emotions; while disgusted faces activated only bilateral occipital face areas[15]. However, this meta-analysis did not control for activation related to cognitive functions non-specific to face processing since it included studies using *any* paradigms involving emotional faces.

The present meta-analysis sought to contribute to the understanding of how discrete emotional face categories relative to neutral faces were processed in the brain. Unlike previous approaches[13-15], our meta-analysis focused on a single paradigm involving passive or active viewing of emotional face and excluded tasks involving additional cognitive function, such as oddball target detection, inhibition or cognitive interference, and mnestic/memorization tasks, to control for non-specific cognitive processes other than that for emotional faces. To update and extend our past approach[12], only whole-brain studies were included to produce an unbiased location of effects. Furthermore, a hierarchical clustering analysis of the meta-analytic maps[16, 17] was used to explore how closely related the processing of one emotional face category was to another.

2. METHODS

2.1. Search strategy

A comprehensive systematic literature search was conducted in the databases EMBASE, MEDLINE and APA PsycINFO using the Ovid® platform, combining key terms related to emotional faces (i.e., “facial emotion*” or “facial affect*” or “affective face*” or “emotional face*” or (happy or happiness or sad or sadness or fear* or anger or angry or disgust* or neutral) ADJ3 face*); and neuroimaging (i.e., “functional magnetic resonance imaging” or “neuroimaging” or fMRI). The search was conducted from the year 2008, when the last meta-analysis conducted in a similar manner on this topic was conducted[12], to 5th October 2021. A manual reference search was conducted through previous meta-analyses to find articles meeting our criteria before the year 2008. The protocol for this meta-analysis was pre-registered in PROSPERO (CRD42022251548). This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 reporting guidelines[18].

2.2. Eligibility criteria

Included studies reported (a) fMRI data during emotional face viewing with whole-brain coverage, which is unbiased toward specific brain anatomical regions[9, 13, 15]; and if they were (b) peer-reviewed empirical research studies involving (c) ≥ 12 healthy participants to reduce the probability of false positive findings as applied in previous meta-analyses[9]. Included studies also reported one of the acceptable fMRI contrasts between emotional faces (i.e., happy, sad, angry, fearful or disgusted) with either (d) a neutral face as primary interest, or a baseline fixation cross as secondary interest in this study. Following our previous meta-analytic approach[12], (e) only studies using a single paradigm assessing emotional processing during the passive or active viewing of emotional human faces were included (i.e., studies using tasks involving additional cognitive functions such as oddball target detection, inhibition or cognitive interference, and mnestic/memorization were excluded). Studies were also excluded (f) if there were no brain activation peak coordinates; or (g) if their samples overlapped with other publications, in which case the study authors were contacted to help decide which study sample should be included in the meta-analysis. Finally, (h) reviews, meta-analyses, and non-peer-reviewed publications were also excluded.

2.3. Study selection

The study selection was assisted by the software EndNote20® (Philadelphia, PA), commenced by a semi-automated removal of duplicates, conference/dissertation abstracts and foreign-language publications pre-screening. Studies were then screened in two stages. The first screening by title and abstract was completed by two independent screeners (LF/SL). The second full-text eligibility screening was completed by three pairs of independent screeners (LF/VO, FG/SL, ET/KW). In both stages, rating discrepancies were discussed to reach a consensus, if necessary, with a third researcher (PFP/SD).

2.4. Data extraction

Data extracted from the studies included (a) sample sizes and characteristics, i.e., mean age, handedness and, percentage of female participants; (b) MRI parameters, i.e., field strength, time repetition (TR), sequence duration, slice thickness, inter-slice gap, whether a whole-brain scan took place; (c) task parameters, i.e., trial numbers/lengths, interval duration between trials, and task design (block *vs.* event-related); (d) neuroimaging analysis information such as pre-processing software (e.g., FSL, SPM), the use of slice timing correction, motion correction, and stereotactic space (e.g., MNI, Brett's mni2tal); and registration methods to the stereotactic space (e.g., nonlinear based on T1), high-pass filtering, smoothing, covariates at first level numbers and reasons for rejected scans, group-level statistics and the statistical threshold. Finally, (e) for each contrast, we extracted the coordinates and effect size statistics (e.g., *T* or *Z* scores) from the peaks of clusters of statistically significant voxels or statistical parametric maps where available. Data were extracted independently by pairs of researchers (LF/VO; FG/SL; ET/KW). Disagreements were discussed to reach a consensus, if necessary, with a third researcher (PFP/SD).

2.5. Quality assessment

Each study was evaluated using a quality assessment tool adapted from a reporting checklist for fMRI studies[19]. Our checklist contains 8 items (see Supplementary Material), each given a score 1 (i.e., clear reporting), 0.5 (i.e., possible reporting bias) or 0 (i.e., evidence for reporting bias); and yields a maximum score of 8. A total score ≥ 6.5 was given a quality rating of 'good', 3.5 to 6 was 'fair', and 3 or below was 'poor'. The assessment was completed independently by pairs of researchers (LF/VO, FG/SL, ET/KW) who discussed their rating disagreements in pairs to reach a consensus, if necessary, with a third researcher (PFP/SD). Studies that were rated poor would be excluded from the meta-analysis.

2.6. Neuroimaging data synthesis

A meta-analytic data synthesis approach was taken using the Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI; www.sdmproject.com). The SDM-PSI enables the synthesis of discrete peaks and effect sizes of clusters of brain activation and continuous statistical parametric maps. Briefly, the SDM-PSI creates a map of voxel-wise Hedges' *g* for each study and then applies a meta-analytic random-effects model. Importantly, the tool allows studies with incomplete data (e.g., only reporting coordinate but not effect size) to include in the meta-analysis, by multiple-imputing Hedges' *g* maps, which are subsequently combined using Rubin's rules. The present SDM-PSI version applies a threshold-free cluster enhancement (TFCE) correction and subject-based permutation tests for multiple comparisons.

The main meta-analyses were conducted for the contrasts between each category of emotion with neutral faces alone, considered an ideal index for tapping emotional processing. Given the frequent use of fixation cross as a baseline condition in emotional face processing studies, meta-analyses were also conducted for contrasts between each emotion with neutral face or fixation cross in combination. These analyses were investigated primarily using a family-wise error rate $p_{FWE}<.05$, but clusters surviving $p_{FWE}<.01$ would also be indicated. Furthermore, we explored clusters at an uncorrected threshold of $p<.005$ if no clusters survived the family-wise error correction to provide readers with a range of statistical significance.

To explore the processing closeness among different emotional categories, we conducted agglomerative hierarchical clustering of the meta-analytic maps contrasting a given emotion with neutral faces. First, pairwise Pearson's *r*s were calculated between unthresholded effect size (Hedge's *g*) maps across all voxels within the SDM mask, which has been shown to best capture the image dissimilarity among SDM meta-analyses[17]. We subsequently calculated the dissimilarity matrix (1-*r* values) and applied agglomerative hierarchical clustering in *R* using the average linkage method[17]. We used bootstrapping to assess the stability of these clusters. Specifically, we used the *pvclust* package for R, which resampled 1000 times the voxels, conducted the cluster analysis for each resample, and counted how many of these resamples showed the original clusters[20].

Further exploratory analyses were conducted when there were sufficient data (approximately 10 studies). First, a meta-analysis was conducted combining all negative emotions (i.e., angry, fearful, disgust, sad[9]) in contrast with neutral faces. A meta-analysis combining only threatening faces (i.e., angry, fearful) against neutral faces was also conducted. Comparative meta-analyses were also conducted pairwise between each emotion category, which was contrasted with neutral faces, for instance, between angry (*vs.* neutral) and happy (*vs.* neutral) faces.

As an additional investigation following previous meta-analyses[15, 21], we investigated the consistency of hemispheric lateralization of emotion processing regions across neuroimaging studies. Lateralization was indicated by a Laterality Index (LI), computed for each emotion using the method outlined by Xu and colleagues[15]. We sought to explore the replication of findings and extracted the average *Hedges' g* values from the right and left amygdala, anterior insula, and ventral medial prefrontal cortex (vmPFC) corresponding to past meta-analyses[15, 21]. Extracted regions followed the automated anatomical labeling (AAL) template[22].

Finally, within each emotional category, sensitivity meta-analyses were conducted with studies involving adult participants, and with those involving implicit tasks only. In addition, meta-regressions were used to examine the association between sex or age with emotional face processing.

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3. RESULTS

3.1. Study selection

The initial search retrieved 5549 studies. After duplicate records, conference & dissertation abstracts and foreign language publications were removed, 1823 studies underwent a title and abstract screening, of which 519 were submitted to a full-text screening. From this subset, 477 studies were excluded, primarily in the absence of appropriate neuroimaging contrasts (n = 158), or a whole-brain analysis (n = 121), leaving 53 studies (i.e., 55 unique datasets) to be included in the meta-analysis (see Fig 1 and Table 1).

--INSERT TABLE 1 ABOUT HERE

3.2. Meta-analyses of emotional face processing

Table 2 shows activations in each emotion relative to neutral faces, alone (Table 2A, Fig. 2A), or in combination with a fixation cross (i.e., "baseline condition"; Table 2B). Findings are reported at the threshold of significance at $p_{FWE}<.05$, which is relaxed to uncorrected $p<.005$

when further exploration is warranted. Table 2 also indicated regions that survived the conservative threshold of p_{FWE}<.01. Unless otherwise stated, all findings showed no significant heterogeneity or publication bias.

Angry

Angry relative to neutral faces contrast (n=21) was associated with activation in R cerebellum/FFA and R middle temporal gyrus (MTG) (Table 2A[i], Fig. 2A[i]) at p_{FWE}<.05. Relative to baseline, angry faces were associated with activation in bilateral cerebellum/FFA, L IFG, R MTG, R inferior occipital gyrus (IOG), and L amygdala (Table 2B[i]) at p_{FWE}<.05. The R IOG cluster showed a significant publication bias (p=.046).

Fearful

Fearful compared to neutral faces contrast (n=27) evoked activation in R ITG/FFA/cerebellum, L putamen/hippocampus/amygdala, R PHG/amygdala (Table 2A[ii], Fig. 2A[ii]) at p_{FWE}<.05. Fearful compared to baseline contrast (n=33) was associated with activation in bilateral cerebellum/FFA, amygdala, SMA, L inferior parietal gyrus (IPG) and left thalamus at p_{FWE}<.05 (Table 2B[ii]).

Disgusted

Disgusted relative to neutral faces contrast (n=8) was associated with increased L MOG activation at p_{FWE}<.05 (Table 2A[iii], Fig. 2A[iii]). Compared to baseline (n=10), disgusted faces were associated with increased activation in L supplementary motor area (SMA) and L superior frontal gyrus (SFG) at p_{FWE}<.05 (Table 2B[iii]). The cluster of activation in SMA had high heterogeneity (I^2>50%) across studies, and a significant publication bias (p<.001).

Happy

Happy relative to neutral faces contrast (n=20) evoked no significant activation at p_{FWE}<.05 (Table 2A[iv], Fig. 2A[iv]), but further exploration using uncorrected p<.005 threshold revealed an activation in L middle occipital gyrus (MOG) and R fusiform area (FFA) (Table 2B[iv]). Happy relative to baseline (n=38) contrast elicited activation in bilateral MOG at $p_{FWE}<.05$.

Sad

Sad compared to neutral faces contrast (n=9), showed no activation, neither at $p_{FWE}<.05$ nor uncorrected $p<.005$ (Table 2A[v]). Sad faces compared to baseline contrast (n=10) showed no activation at $p_{FWE}<.05$, but further exploration revealed higher activation in L insula at uncorrected $p<.005$ (Table 2B[v]).

Neutral face vs. fixation cross

Neutral faces, relative to a fixation cross, evoked activation in the R SMA, cerebellum, putamen, left postcentral gyrus, R IFG, and L hippocampus at $p_{FWE}<.05$.

--INSERT TABLE 2 ABOUT HERE

3.3. Hierarchical clustering analyses

Pairwise correlations between meta-analytic maps across emotional categories (Fig. 2B) were in the lower moderate range (*r*s = 0.3-0.4), except between angry and fearful faces which was higher moderate (*r* = 0.47) and between sad and any other emotional faces which was in the low range (*r*s = -0.1-0.2). Thus, the dendrogram first merged for the processing of angry and fearful faces (cophenetic distance *d* = 0.53), which were subsequently merged with the processing of disgust and happy faces (*d*s = 0.64-0.66). The sad face processing was not merged until the top of the dendrogram (*d* = 0.93). The activation clusters of angry and fearful faces were differentiated from those of the disgust faces with 100% probabilities. The activation clusters of disgust faces were differentiated from those of happy faces with 73% probabilities. Finally, the activation clusters of happy faces were differentiated from those of sad faces with 100% probabilities.

3.4. Meta-analyses of emotion groups

Negative emotional faces

Negative emotion relative to neutral faces contrast (n=40) evoked increased activation in bilateral cerebellum/FFA, L IFG, L SFG, R putamen/amygdala, and L MTG (Fig. 2C[i], supplementary Table S2). Negative relative to baseline (n=51) was associated with increased activation in the bilateral cerebellum/FFA, R pre-central gyrus/amygdala, L IFG, L SFG, R MTG, L post-central gyrus, and R median cingulate/paracingulate gyrus.

Threatening emotional faces

Threatening relative to neutral faces contrast (n=35) evoked increased activation in bilateral cerebellum/FFA, L IFG, bilateral putamen/amygdala, and R MTG and R precentral gyrus at $p_{FWE}<.05$ (Fig. 2C[ii], supplementary Table S3). Threatening relative to baseline faces contrast (n=46) evoked increased activation in the bilateral cerebellum/FFA, R pre-central gyrus/amygdala, L IFG, L SFG, R MTG, L post-central gyrus, and R median cingulate/paracingulate gyrus at $p_{FWE}<.05$.

--INSERT FIG 2 ABOUT HERE

3.5. Exploratory pairwise comparisons between emotional contrasts

Negative emotion categories vs. happy faces

Relative to happy faces, angry faces were associated with activation in R MTG and L IFG, disgusted faces were associated with activation in L IFG and R putamen, and fearful faces were associated with activation in R ITG, R precentral gyrus, and R putamen/insula, whereas sad faces were associated with deactivation in bilateral MOG and R FFA, all at $p_{FWE}<.05$ (Supplementary Fig. S1A, Table S2).

Pairwise comparisons among negative emotional faces

When comparing pairwise between the negative emotion vs. neutral face contrasts (Supplementary Fig. S1B, Table S3) we found that angry faces showed increased activation in R MTG compared to disgusted or fearful faces at p_{FWE}<.05. Angry faces also showed increased activation in bilateral IOG, R FFA, R STG, L MFG, L lingual gyrus and R MTG compared to sad faces at p_{FWE}<.05. Disgusted faces compared to fearful faces showed decreased activation in the R ITG; and compared to sad faces, they showed increased activation in the SMA, L MOG, R putamen, and L IFG. Finally, fearful, relative to sad faces, were associated with increased activation in the bilateral FFA, PHG and amygdala, right precentral gyrus, and left IOG at p_{FWE}<.05.

3.6. Hemispheric lateralization of activation

Amygdala activation was left-lateralized during the processing of all emotion categories. Activation of AI also showed left hemispheric lateralization during the viewing of all emotional but disgusted faces, which showed no lateralization, or happy faces, which showed right lateralization. Meanwhile, vmPFC showed a right dominance for processing all negative emotions but left hemispheric lateralization in response to happy faces (Fig 3 and supplementary Table S4).

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3.7. Other exploratory meta-analyses

Sensitivity meta-analyses involving adult participants or implicit tasks

No significant brain activation was found in sensitivity meta-analyses involving subgroups of adult participants or implicit tasks within each emotional category.

Meta-regressions with age and sex within each emotion category

No significant association was observed between age or sex and each category of emotional face processing.

3.8. Quality assessment ratings

Among the included studies, 31 (58.5%) of them were rated “good” while the remaining were “fair”. No studies were rated poor (Supplementary Fig. S2). Therefore, all studies were included in the meta-analysis.

4. DISCUSSION

Theories of emotional face processing relied on findings from studies involving the processing of broad emotional stimuli and tasks that might be influenced by other cognitive functions. This meta-analysis focused on studies that compared emotional versus neutral faces using a single passive or active emotional face viewing paradigm. Our primary findings showed extensive activation clusters by fearful relative to neutral faces in the right ITG, right FFA, left putamen/amygdala, right PHG and cerebellum. Fewer activation clusters were evoked by angry relative to neutral faces in the right cerebellum and right MTG and by disgusted faces in the left MTG. Happy and sad relative to neutral expressions did not evoke activation beyond the main threshold of significance. However, an exploration using a less conservative uncorrected threshold of $p < 0.005$ revealed that happy faces evoked activation in left MOG and right FFA. Fearful and angry faces appeared to have the highest meta-analytic map correlation and shortest cophenetic proximity, while happy and sad faces had the lowest correlation, and highest distance, to any other emotional faces.

Different emotions evoke primarily discrete clusters of activation in this study. Among the different emotional face categories, fearful faces appear uniquely associated with amygdala activation, which corresponds to the idea that the amygdala is more sensitive toward, and is more strongly activated by, fearful faces than any other emotion[12, 76, 77]. We also found that fearful faces evoked the most extensive clusters of activation in the brain, which is similar to findings from a recent meta-analysis of whole-brain studies of the emotional relative to neutral faces[15]. Such wide-ranging activation may reflect a heightened vigilance and arousal supporting the readiness for flight-or-fight responses[78, 79].

Notable findings are the overlaps of several activation clusters (i.e., cerebellum and closely neighboring posterior-temporal regions) during the processing of fearful and angry faces, and the closest proximity of these two emotions in the novel hierarchical clustering analysis. Furthermore, the cerebellum, neighboring posterior-temporal regions and amygdala were all activated when we investigated the processing of fearful and angry faces in combination compared to neutral faces. This functional similarity is presumably related to the threats conveyed by both emotional faces, whether it is inferred from a third-person perspective in the case of fearful faces, or directly experienced by the observer of an angry face. The cerebellum plays an important role in fear learning and mediating motor response to threats[80, 81] and its stimulation enhances the perception of threat faces[82]. The activation of posterior temporal cortices might be related to the engagement of the theory of mind network to assess the intention of a potential perpetrator[17, 83].

Disgusted faces elicited activation in the left MOG, partly replicating previous findings in the bilateral MOG[15]. However, unlike previous findings of activation in the left amygdala by sad and happy faces[15], no consistent brain response to these facial emotions was observed in the present study. These discrepant findings may be related to the specificity of the eligible task in the present study, and it may also indicate that these effects were weaker in magnitude, such that they were undetectable with the inclusion of fewer studies in this meta-analysis.

The meta-analytic maps of emotional categories, which show “imperfect correlation” of weak to moderate-strong magnitude, point towards an underlying general neural response during emotional face processing as theorized by the constructionist model[8], although the spatial response patterns seem emotion-specific. In the context of the theories of emotional face processing, however, our most interesting finding was the lack of consistent amygdala activation during the processing of emotional faces other than fearful faces, and the hierarchy of cophenetic proximities that leads to early agglomerative clustering of threat-related activation by fearful and angry faces. These findings show that the human brain orients its response to emotional faces based on the *absence* or the *presence* of threats, the latter of which receives processing priority. This may explain why happy and sad faces - which convey the *absence* of a potential *threat*, and additionally for sad faces, the *presence* of *vulnerability* - evoke the less response and show the weaker meta-analytic map correlation in relation to fearful and angry faces.

Negative emotional faces (fearful, angry, disgusted, sad) relative to neutral faces were associated with activation in the right amygdala, temporal and fusiform cortices, corresponding to previous meta-analytic findings[9, 15], which extended to the cerebellum – presumably driven by responses to the angry and fearful faces – and to the left inferior/superior frontal cortices. The additional comparison of threatening (angry, fearful) relative to neutral faces, that we conducted following the hierarchical clustering analyses, found evoked activation in highly overlapping areas in bilateral putamen/amygdala and cerebellum/FFA, left IFG and right MTG and right precentral gyrus, indicating the predominant contribution of threatening faces in activation clusters observed in the contrast between negative emotion to neutral faces. Furthermore, exploratory pairwise meta-analytic comparisons among facial emotion categories (Supplement Fig S1) elucidate the activation clustering elicited by these five emotion categories, where angry or fearful faces evoke the most pervasive pattern of activation when compared with happy and particularly sad faces, which are the furthest in the cophenetic distance. Overall, our findings support the view that emotions are processed in a latent grouping as previously suggested[9], but this grouping is based on threat content rather than valence.

Laterality effects were investigated in the amygdala, anterior insula, and vmPFC, following previous studies[15, 21]. There are two classic hypotheses of brain lateralization of emotional processing. The right-hemisphere dominance theory proposes that all emotions are predominantly processed in the right brain hemisphere[21, 84], while the valence lateralization hypothesis proposes a left hemispheric specialization in processing positive/approach-related emotions, and a right-lateralized processing of negative/withdrawal emotion, particularly in the frontal area[85, 86].

Our findings provide little support for an absolute right-hemisphere dominance of emotional face processing[21, 84]. Evoked activation across all emotional categories was exclusively left-lateralized in the amygdala, or predominantly left-lateralized in the anterior insula. The exclusively left-lateralized processing of emotional faces in the amygdala is in line with conclusions of some reviews and meta-analyses[15, 87] but not of others, including our previous meta-analytic attempt[12, 21, 84, 88, 89]. The different findings might be related to the exclusion of studies involving subliminal or subconscious perception of unattended emotional faces, that are thought to be associated with right amygdala activation dominance[88, 89]. The anterior insula activation, which is predominantly left-lateralized during perception of nearly all emotional faces but happy faces that are right-hemisphere dominant, only partly replicates recent findings[15]. Specifically, the right-lateralized anterior insular response to happy faces contradicts a previous meta-analytic finding that has shown left-lateralized insula activation by positive emotions[90], although the inclusion of studies involving emotional experience as well as emotional face perception in the past meta-analysis may have confounded the laterality of findings. Interestingly, lesion studies have shown an association between left-hemispheric insular lesions with emotional face recognition[91, 92] and an association between right anterior insula lesions with happy and angry face recognition[93], although the emotional- or regional-specificity of these association were not always examined. Finally, activation in the vmPFC is predominantly right-lateralized for all emotion categories, which also partly replicates recent findings[15], except for the processing of happy faces which is left-lateralized. The frontal pattern of asymmetry in this region is thus in line with the valence hypothesis[85]. Overall, our findings suggest a general pattern of left-lateralized activation in the amygdala and insula, and right-lateralized activation in the vmPFC. The variation to this general pattern should be taken with caution due to the relatively few studies included in the meta-analyses. Taken together, our findings show that the processing of emotional faces is more complex than previously existing theories have proposed.

Finally, several studies used fixation cross as a control condition for emotional faces when investigating emotional face processing. Our meta-analysis shows that neutral faces evoke non-negligible activation in prefrontal, subcortical and cerebellar areas when compared to fixation cross. Furthermore, including studies with fixation cross as a control condition leads to the presence of more activation clusters for each emotion compared to neutral faces alone, presumably due to the recruitment of regions associated with processing of facial features unrelated to emotion. Our findings demonstrate the need to control for processes related to the general face perception when studying the processing of each emotional category of faces.

Our findings should be viewed in consideration of their limitations and strengths. As with any other imaging meta-analyses, the reliance on discretized effect sizes based on peak coordinate location instead of statistical brain maps, and the varying level of statistical threshold reporting from original studies could lead to under-detection of smaller clusters of activation. At an uncorrected significance threshold, the activation in the left MOG and right FFA during the viewing of happy relative to neutral faces should be considered a preliminary finding and will require confirmation from future meta-analyses. The decision to limit our scope to a single paradigm involving the viewing of emotional faces in this meta-analysis resulted in the inclusion of relatively fewer studies, which further constrained the power to detect smaller effects. This may explain why we found no influences of age or sex in the emotional processing activation in the meta-regression analyses. However, this choice of method also enhances the specificity of our findings to brain activation related to emotional face processing only, controlling for non-specific cognitive processes beyond passive or active emotional face viewing.

5. CONCLUSION

This meta-analysis is among the few that specifically investigate the processing of discrete emotional face categories relative to neutral faces[12, 15], but focused on studies involving the viewing of emotional faces only. The primary findings suggest that the processing of emotional faces in the human brain is oriented to prioritize the identification of threats (i.e., fearful and anger faces) over non-threatening emotional categories (i.e., happy and sad faces), with a more complex lateralization pattern than previously existing theories have proposed. This appears to support the view that emotional faces are processed in latent grouping, by threats content rather than valence, which provides a novel way for theorizing how emotional faces are processed in the human brains.

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7. CONFLICTS OF INTEREST

PFP has received research funds or personal fees from Lundbeck, Angelini, Menarini, Sunovion, Boehringer Ingelheim, Proxymm Science, outside the current study. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

8. AUTHORS CONTRIBUTION

SL & LF: Contributed substantially to conception and design, acquired, analyzed and interpreted the data; drafted the article and critically revised it for important intellectual content; and gave final approval of the version to be published. FG, KZW & ET: Contributed substantially to acquisition of data, critically revised the article for important intellectual content, and gave final approval of the version to be published. VO: Contributed substantially to acquisition and analyses of data, critically revised the article for important intellectual content, and gave final approval of the version to be published. SD: Contributed substantially to acquisition and interpretation of the data; critically revised the article for important intellectual content; and gave final approval of the version to be published. JR: Contributed substantially to conception and design, analysed and interpreted the data; critically revised the article for important intellectual content; and gave final approval of the version to be published. PFP: Contributed substantially to conception and design, interpreted the data; critically revised the article for important intellectual content; and gave final approval of the version to be published.

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Table 1. Characteristics of included studies

Studies	n (% female)	Age, years; Mean (SD)	Scanner Magnetic Field (T)	Task design	Face paradigm	Emotion condition	Control condition	Implicit response
Arsalidou et al. (2011)[23,a]	15 (86.7)	26.3 (4.5)	1.5	BD	MacBrain	Angry	Fixation	Y
Arsalidou et al. (2011)[23,b]	24 (75.0)	26.5 (4.6)	1.5	BD	MacBrain	Happy	Fixation	Y
Azuma et al. (2015)[24]	14 (35.7)	13.0 (3.0)	1.5	ER	Emotional	Disgust, Fearful, Neutral	Fixation	Y
Batut et al. (2006)[25]	15 (60.0)	N/A (N/A)	2	BD	KDEF	Fearful, Happy, Sad	Neutral	Y
Chan et al. (2016)[26]	54 (61.0)	23.0 (2.4)	1.5	BD	Ekman	Angry, Neutral	Neutral	Y
Daly et al. (2010)[27]	14 (0.0)	28.0 (10.0)	1.5	ER	Emotional	Happy, Fearful, Disgust, Sad, Neutral	Fixation	Y
Davies et al. (2020)[28]	19 (42.0)	23.9 (4.2)	3	ER	Emotional	Fearful	Neutral	Y
de Greck et al. (2012)[29]	20 (55.0)	23.0 (N/A)	3	BD	Ekman	Angry, Neutral	Fixation	N

Del-Ben et al. (2012)[30]	12 (0.0)	24.8 (3.2)	1.5	BD	Ekman	Happy, Fearful, Angry	Neutral	Y
Domes et al. (2010)[31]	16 (100.0)	24.2 (2.5)	1.5	BD	Emotional	Fearful, Angry	Neutral	N
Faivre et al. (2012)[32]	18 (67.0)	N/A (N/A)	3	BD	Ekman	Happy	Neutral	Y
Fischer et al. (2005)[33]	22 (50.0)	74.1 (3.8)	1.5	ER	Ekman	Angry	Neutral	Y
Grosbras and Paus (2006)[34]	20 (50.0)	28.6 (N/A)	1.5	BD	Emotional	Angry, Neutral	Fixation	Y
Haller et al. (2018)[35]	25 (60.0)	14.0 (2.2)	3	BD	Ekman	Happy, Fearful, Angry	Neutral	Y
Hoehl et al. (2010)[36]	18 (50.0)	24.0 (N/A)	3	ER	NimStim	Happy, Angry	Fixation	Y
Hornboll et al. (2013)[37]	23 (39.0)	31.8 (6.5)	3	BD	Emotional	Fearful, Angry	Neutral	Y
Ihme et al. (2014)[38]	48 (47.9)	24.0 (3.0)	3	ER	KDEF	Happy, Fearful, Angry	Neutral	N
Jehna, Langkammer, et al. (2011)[39]	15 (66.7)	30.3 (10.6)	3	BD	KDEF	Fearful, Angry, Disgust	Neutral	Y
Jehna, Neuper, et al. (2011)[40]	30 (70.0)	36.3 (14.3)	3	BD	KDEF	Fearful, Angry, Disgust	Neutral	Y
Jones et al. (2009)[41]	13 (0.0)	11.3 (0.92)	3	BD	Ekman	Fearful	Neutral	Y
Kempton et al. (2009)[42]	74 (45.9)	34.9 (13.7)	1.5	ER	Ekman	Fearful	Neutral	N

Kersting et al. (2009)[43]	12 (100.0)	30.6 (4.2)	3	BD	Ekman	Happy	Neutral	N
Lassalle et al. (2017)[44]	21 (0.0)	19.7 (7.7)	3	BD	MacBrain	Happy, Fearful, Angry	Neutral	Y
Lee et al. (2013)[45]	29 (0.0)	N/A (N/A)	3	BD	Ekman	Angry	Fixation	N
Lee et al. (2017)[46]	18 (22.3)	39.3 (12.6)	3	Mixed	Ekman	Angry	Neutral	Y
Lee et al. (2008)[47]	13 (0.0)	24.8 (3.6)	1.5	BD	N/A	Happy, Sad	Neutral	Y
Lennox et al. (2004)[48]	12 (50.0)	32.6 (10.7)	3	ER	FEEST	Happy, Sad	Neutral	N
Mallorqui-Bague et al. (2015)[49]	51 (64.7)	33.3 (4.9)	3	ER	N/A	Sad	Neutral	Y
Marchand et al. (2011)[50]	19 (0.0)	33.7 (12.5)	3	BD	Ekman	Happy	Neutral	Y
McCloskey et al. (2016)[51]	20 (40.0)	32.8 (N/A)	3	BD	Ekman	Happy, Angry	Neutral	N
Miskowiak et al. (2008)[52]	12 (41.7)	23.7 (6.2)	1.5	BD	Ekman	Happy, Fearful, Neutral	Fixation	Y
Morawetz et al. (2016)[53]	48 (52.1)	29.7 (11.1)	3	Mixed	Emotional	Angry	Neutral	N
O'Nions et al. (2011)[54]	30 (43.4)	26.6 (6.0)	3	BD	N/A	Happy, Fearful	Neutral	Y

Palm et al. (2011)[55]	16 (100.0)	34.0 (13.0)	1.5	BD	Ekman	Happy, Angry, Fearful, Sad	Neutral	Y
Park et al. (2021)[56]	230 (62.6)	39.4 (12.8)	3	BD	Emotional	Happy, Angry, Fearful, Sad, Disgust	Neutral	N
Park et al. (2016)[57]	17 (52.9)	23.1 (3.9)	3	BD	Emotional	Happy, Fearful, Neutral	Fixation	Y
Passamonti et al. (2012)[58]	19 (47.4)	24.5 (3.3)	3	BD	MacBrain	Angry, Sad	Neutral	Y
Rauch et al. (2007)[59]	20 (50.0)	N/A	3	BD	Ekman	Happy, Angry, Fearful	Neutral	Y
Reidy et al. (2016)[60]	15 (0.0)	8.7 (1.1)	3	ER	NimStim	Happy, Angry, Fearful, Disgust	Neutral	Y
Sambataro et al. (2006)[61]	24 (54.2)	26.8 (5.6)	3	BD	Emotional	Disgust	Neutral	Y
Spencer et al. (2011)[62]	40 (50.0)	15.1 (1.6)	3	BD	Ekman	Happy, Fearful	Neutral	Y
Spilka et al. (2015)[63]	27 (51.9)	40.7 (11.1)	3	ER	Emotional	Happy, Angry Fearful, Sad	Neutral	N
Stevens et al. (2013)[64]	20 (100.0)	41.1 (10.7)	3	BD	Ekman	Fearful	Neutral	N
Surguladze et al. (2010)[65]	20 (50.0)	41.9 (11.6)	1.5	ER	FEEST	Happy, Fearful, Neutral	Fixation	Y

Tamm et al. (2020)[66]	72 (55.6)	44.0 (N/A)	3	BD	KDEF	Happy, Angry	Neutral	Y
Trautmann et al. (2009)[67]	16 (100.0)	21.6 (2.3)	3	BD	Emotional	Happy, Disgust	Neutral	Y
van den Bulk et al. (2013)[68]	27 (88.9)	14.6 (1.6)	3	BD	NimStim	Happy, Fearful, Neutral	Fixation	Y
Vuilleumier et al. (2001)[69]	12 (50.0)	27.7 (N/A)	2	ER	N/A	Fearful	Neutral	Y
Vuilleumier et al. (2004)[70]	13 (46.2)	35.9 (8.6)	2	ER	N/A	Fearful	Neutral	Y
Wabnegger et al. (2015)[71]	22 (50.0)	51.8 (98)	3	BD	KDEF	Angry, Disgust, Fearful, Sad	Neutral	Y
Wicker et al. (2003)[72]	14 (0.0)	N/A (N/A)	3	BD	Video	Happy, Disgust	Neutral	Y
Williams et al. (2004)[73]	22 (36.4)	27.2 (8.1)	1.5	BD	N/A	Fearful	Neutral	Y
Williams et al. (2006)[74]	15 (53.4)	35.8 (9.1)	1.5	BD	Gur	Fearful	Neutral	Y
Zsoldos et al. (2016)[75,c]	17 (47.1)	68.6 (5.6)	3	ER	KDEF	Fearful	Neutral	Y
Zsoldos et al. (2016)[75,d]	17 (60.0)	24.9 (2.7)	3	ER	KDEF	Fearful	Neutral	Y

Abbreviations. BD=block-design task, ER=event-related task, FEEST=facial expressions of emotion: stimuli and tests, KDEF=Karolinska directed emotional faces, n=number, N/A=not available, SD=standard deviation, Y/N=yes/no. [a, b] different experimentation in the same study, [c,]

[d] older and younger adult datasets, [e] neutral faces were always contrasted with fixation cross, while other categories of emotional faces might be contrasted with either neural faces or fixation cross. Summary findings are in supplementary Table S1.

Table 2. Meta-analytic findings of processing of emotional *vs.* neutral faces or baseline

	Peak					Cluster	
	MNI	Hedge's *g*	*Z*-value	I^2	*p*-value	Voxels	Breakdown
(A) Emotional *vs.* neutral faces							
(i) Angry *vs.* neutral							
R FFA	40,-54,-18	0.306	5.796	2.4	<.0001	867	R cerebellum (486)
							R FFA (294)
R MTG	56,-62,2	0.264	4.870	7.1	.001	381	R MTG (323)
(ii) Fearful *vs.* neutral							
R ITG*	52,-54,-20	0.263	5.125	13.2	.002	970	R FFA (335)
							R ITG (284)
							R cerebellum (273)
L putamen*	-32,-4,-4	0.254	3.388	25	.017	820	L amygdala (132)
							L STG (113)
							L putamen (55)
R PHG	18,-6,-26	0.241	4.010	24	.030	156	R PHG (46)
R cerebellum	32,-72,-20	0.176	3.846	2	.023	114	R cerebellum (96)

(iii) Disgusted *vs.* neutral							
L MOG	-34,-90,0	0.249	2.560	10.7	.038	111	L MOG (86)
(iv) Happy *vs.* neutral							
L MOG‡	-20,-94,14	0.23	4.21	8.7	<.0001	343	L MOG (151)
R FFA‡	36,-74,-16	0.22	4.35	0.9	<.0001	257	R FFA (121)
(v) Sad *vs.* neutral							
Nil.							
(B) Emotions *vs.* baseline (mixed neutral faces/fixation cross)							
(i) Angry *vs.* baseline							
R cerebellum*	34,-66,-26	0.298	6.373	7.8	<.0001	2068	R cerebellum (953)
							R FFA (638)
							R ITG (190)
L IFG*	-40,26,-2	0.218	5.046	0.9	.002	1267	L IFG (981)
							L insula (107)
L cerebellum*	-10,-76,-12	0.204	4.482	6.6	.005	1092	L MOG (361)
							L cerebellum (281)
							L IOG (107)

							L lingual gyrus (106)
R MTG*	56,-62,2	0.250	5.621	4.4	.001	905	R MTG (744)
R IOG*	38,-86,-4	0.286	4.495	48.7	.003	714	R MOG (320)
							R IOG (176)
L amygdala*	-30,-6,-14	0.252	5.413	10.1	.004	209	L amygdala (36)

(ii) Fearful *vs.* baseline

R cerebellum*	34,-46,-24	0.257	5.668	6.6	<.0001	15992	R cerebellum (2550)
							R IFG (1893)
							R FFA (1134)
							R pre-CG (786)
							B lingual gyrus (739)
							R IOG (672)
							R ITG (566)
							R insula (564)
							R PHG (483)
							R MOG (436)
							R putamen (303)
							R post-CG (252)
							R STG (227)

							R rolandic operculum (208) R amygdala (194) R hippocampus (193) R MFG (159) R striatum (106)
L IFG*	-50,18,18	0.268	5.416	12.8	<.0001	5644	L IFG (1635) L STG (498) L insula (429) L PHG (336) L striatum (295) L putamen (257) L hippocampus (214) L amygdala (197) L rolandic operculum (102)
L SMA*	0,18,56	0.268	4.877	28.2	<.0001	2391	B median cingulate/ paracingulate (846) B SMA (821) B SFG (419)

							B ACC/paracingulate (364)
L FFA*	-36,-66,-14	0.228	5.151	1.7	<.0001	970	L FFA (460)
							L cerebellum (227)
							L IOG (217)
L IPL*	-42,-42,52	0.250	4.790	14.3	<.0001	875	L IPL (512)
							L post-CG (285)
L thalamus*	-6,-8,8	0.199	3.873	7	.009	177	L thalamus (34)

(iii) Disgust *vs.* baseline

L SMA	-4,6,54	0.576	2.887	84.4	.029	341	B SMA (321)
L SFG	-2,46,24	0.225	3.249	1.2	.028	142	B SFG (118)

(iv) Happy *vs.* baseline

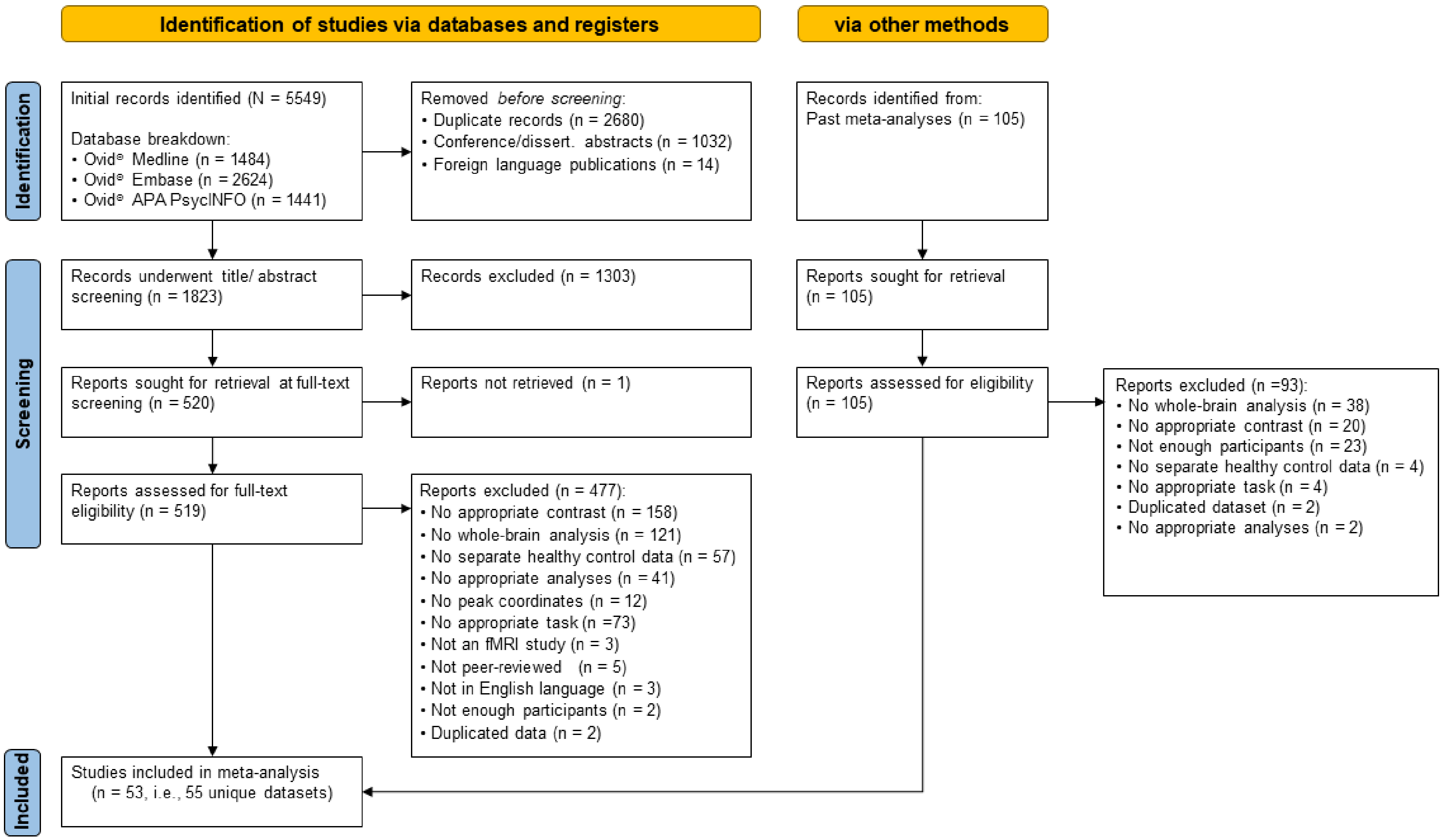
R MOG*	44,-82,2	0.218	4.890	2.5	<.0001	1732	R FFA (404)
							R MOG (283)
							R IOG (217)
							R cerebellum (179)
L MOG*	-18,-96,14	0.241	4.662	4.3	<.0001	872	L MOG (204)
							L cerebellum (109)

(v) Sad *vs.* baseline

L insula[‡]	-38,18,0	0.256	3.872	2.8	<.0001	107	L insula (78)

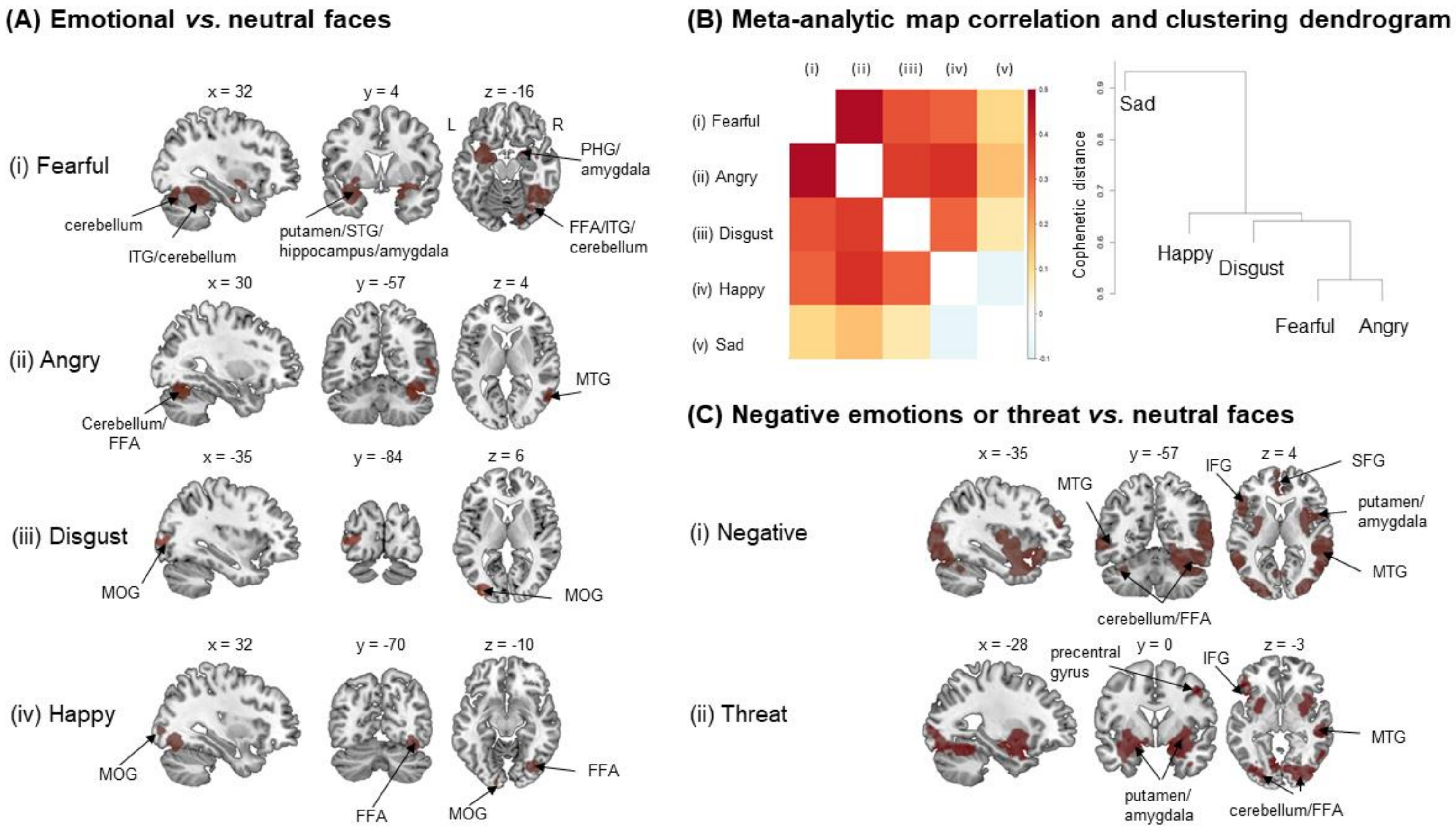
Abbreviation. ACC=anterior cingulate cortex, FFA=fusiform area, IFG=inferior frontal gyrus, IOG=inferior occipital gyrus, IPL=inferior parietal lobule, ITG=inferior temporal gyrus, MFG=middle frontal gyrus, MNI=Montreal Neurological Institute-Hospital, MOG=middle occipital gyrus, MTG=middle temporal gyrus, PHG=parahippocampal gyrus, pre-/post-CG=pre-central gyrus, SFG=superior frontal gyrus, SMA=supplementary motor area, STG=superior temporal gyrus. p_{FWE}=family-wise error corrected threshold of significance. Clusters are reported at the threshold of significance $p_{FWE}<.05$. Clusters that are significant at $p_{FWE}<.05$ and remaining significant at $p_{FWE}<.01$ are indicated with an *. Clusters that are not significant at $p_{FWE}<.05$ but is significant at an exploratory threshold of uncorrected $p<.005$ are indicated with an ‡.

Fig 1. PRISMA Flow Diagram of Study Selection



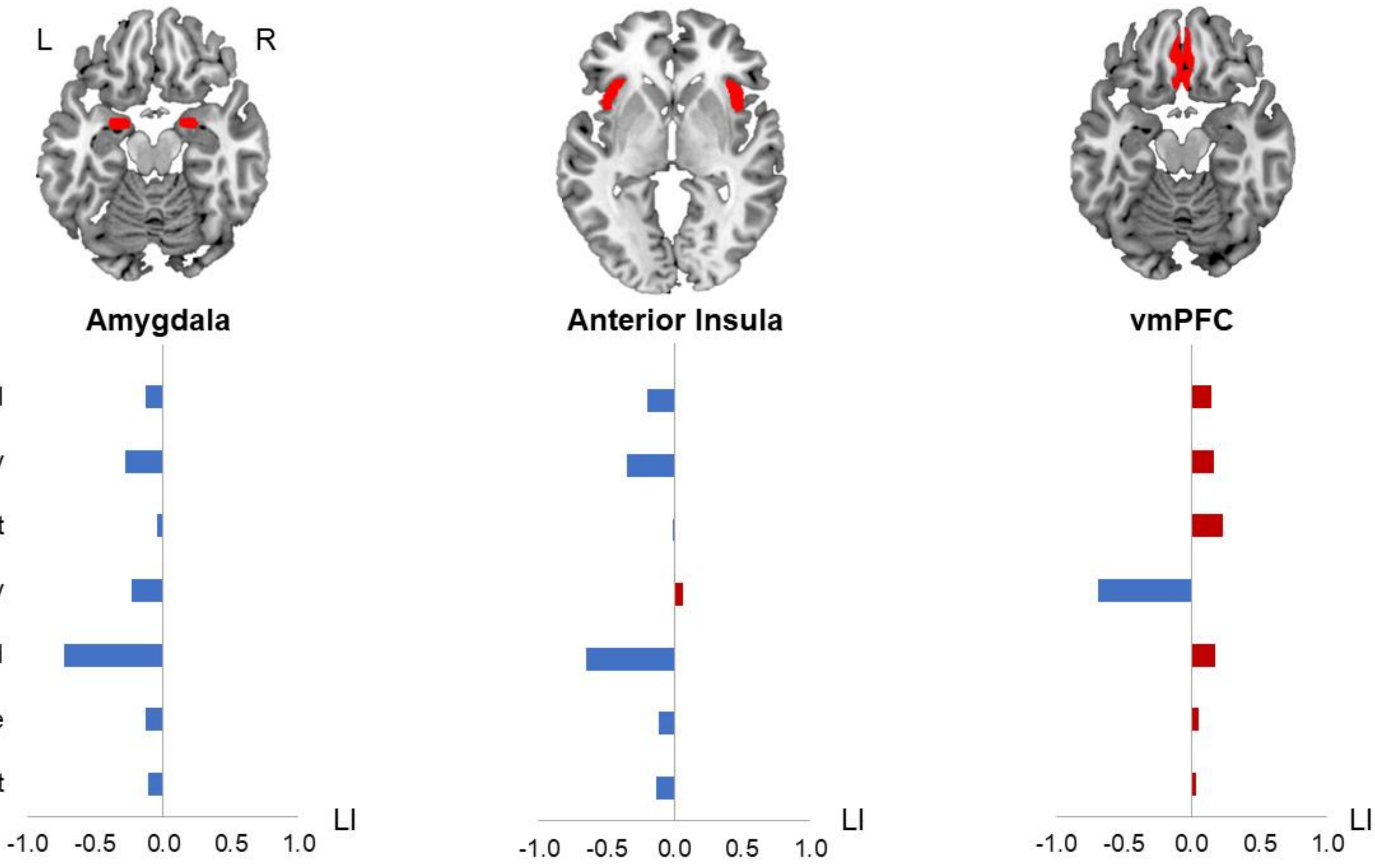
The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram was obtained from http://www.prisma-statement.org/PRISMAStatement/FlowDiagram

Fig 2. Meta-analytic clusters of activations and hierarchical agglomerative clustering of meta-analytic maps



Abbreviation. IFG = inferior frontal gyrus, ITG = inferior temporal gyrus, FFA = fusiform face area, MOG = middle occipital gyrus, MTG = middle temporal gyrus, PHG = parahippocampal gyrus, SFG = superior frontal gyrus, STG = superior temporal gyrus. (A) meta-analytic activation clusters in each emotional face category contrasted with neutral faces ([i]-[iii] activation clusters were significant at p_{FWE} =.05, [iv] clusters were significant at *p* = .005, uncorrected); (B) meta-analytic maps and clustering dendrogram showed that fearful and angry faces were most similar among other emotional categories; (C) meta-analytic grouping of negative emotions (i.e., fearful, angry, disgusted and sad [i]), and of threatening faces (i.e., fearful and angry [ii]), contrasted with neutral faces.

Fig 3. Hemispheric laterality of brain activation in amygdala, anterior insula and vmPFC



Abbreviation. LI = laterality index, L/R= left/right hemisphere, vmPFC = ventromedial prefrontal cortex. The laterality index approaches to -1 (blue-coloured) when it is left-lateralised, and it approaches 1 (red-coloured) when it is right-lateralised.

1