Activation network mapping for integration of heterogeneous fMRI findings

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Functional neuroimaging techniques have been widely used to probe the neural substrates of facial emotion processing in healthy people. However, findings are largely inconsistent across studies. Here, we introduce a new technique termed activation network mapping to examine whether heterogeneous functional magnetic resonance imaging findings localize to a common network for emotion processing. First, using the existing method of activation likelihood estimation meta-analysis, we showed that individual-brain-based reproducibility was low across studies. Second, using activation network mapping, we found that network-based reproducibility across these same studies was higher. Validation analysis indicated that the activation network mapping-localized network aligned with stimulation sites, structural abnormalities and brain lesions that disrupt facial emotion processing. Finally, we verified the generality of the activation network mapping technique by applying it to another cognitive process, that is, rumination. Activation network mapping may potentially be broadly applicable to localize brain networks of cognitive functions.

Facial emotion processing is a basic capacity of the human brain and plays a crucial role in normal social functioning. It is also the most thoroughly investigated psychological function and a widely used experimental paradigm for studying the neural basis of human emotion. However, controversy remains regarding how emotions are represented in the nervous system. Among them, a major debate has centered on whether different emotions (for example, anger, fear and sadness) have their respective characteristic and discriminable neural signatures (termed ‘basic emotion theory’) or whether they emerge from the combination of shared basic psychological function units and corresponding neural components (termed ‘conceptual act theory’).

Over the last two decades, functional neuroimaging techniques have been widely used to study the neural substrate of facial emotion processing. However, like many other mental functions, functional neuroimaging studies of facial emotion processing are plagued with low reproducibility due to such factors as variability in study design and subject characters, flexibility in data collection, analysis and reporting, and low statistical power.

The prevailing definition of reproducibility in functional neuroimaging studies is mainly based on whether the same brain regions are activated, ignoring connections between them. However, an increasing number of studies indicate that brain functions better localize to connected networks than to isolated brain regions. Similar to the view of Darby et al. that heterogeneous structural neuroimaging findings of the same neuropsychiatric diseases and symptoms localize to a common network, we propose that reproducibility in functional neuroimaging studies should also be redefined in terms of the brain connectivity network. We hypothesize that the seemingly poor reproducibility of functional neuroimaging findings in healthy individuals localizes, in reality, to a highly reproducible network of connected brain regions and that many of the heterogeneous brain activations found in different studies are part of the same network.

To identify the brain network underlying particular symptoms in brain-lesioned patients, a recently developed technique termed lesion network mapping (LNM) has been widely used. LNM uses brain lesions as seeds to derive the brain network of specific symptoms based on a large cohort of resting-state normative connectomes. This technique has been further extended by replacing brain lesions with coordinates of brain structural atrophy and brain stimulation sites as seeds. Adapted from this technique, we propose a new technique termed ‘activation network mapping’ (ANM, Fig. 1) to identify the brain network of facial emotion processing in healthy individuals. Specifically, we used the reported activation coordinates as seeds to identify functional networks based on independent normative resting-state functional magnetic resonance imaging (fMRI) connectomes from large healthy cohorts. Such a technique is biologically plausible because (1) functional neural activations between remote brain regions are strongly interrelated or functionally connected via the mechanism of ‘activity flow’ and (2) resting-state network architecture highly resembles the task-evoked network architecture at both the individual subject level and group level.

In the present study, we used the ANM technique to localize the network substrate of facial emotion processing. First, by dividing experiments into different emotions, we tested whether heterogeneous brain activations across different experiments would localize to a common network within each emotion. Second, we tested whether the identified networks of each emotion support basic emotion theory or the competing conceptual act theory. Third, we pooled experiments of all emotions together to localize an emotion-general expression processing network and assessed the specificity of this network by comparison with control cognitive processes. Fourth, we tested whether our localization of facial emotion processing aligned with transcranial magnetic stimulation (TMS) stimulation sites and brain lesions that disrupt facial...
emotion processing, as well as structural abnormalities in alexithymia, a disorder characterized by a deficiency in the ability to identify emotions. Finally, we tested the generalizability of our technique by applying it to another cognitive process, that is, rumination.

**Results**

Functional neuroimaging studies of facial emotion processing were identified by a literature search of PubMed. Search terms consisted of a combination of three types of keywords: emotion categories (such as happy, fear and sad); stimuli (such as face and expression) and technique (such as fMRI and neuroimaging). The main inclusion criteria were as follows: (1) used neutral faces as control stimuli, (2) involved healthy adult participants, (3) used emotional facial stimuli, (4) reported whole-brain results in Talairach or Montreal Neurological Institute (MNI) space and (5) included activation coordinates. Finally, a total of 141 studies with 230 experiments including 3,138 participants were included in our study (Table 1, Supplementary Table 1 and Supplementary Fig. 1).

**Activation likelihood estimation (ALE) and ANM analyses of individual basic emotions.** The ALE meta-analysis was carried out on five basic emotions: anger, disgust, fear, happiness and sadness. We did not perform the analysis on ‘surprise’ due to its extremely small number of experiments \( n = 4 \). The ALE meta-analytic results show that, within each basic emotion, some brain regions, including the amygdala, fusiform gyrus, medial temporal gyrus, middle occipital gyrus, middle frontal gyrus and inferior frontal gyrus, do engage more often than by chance (Fig. 2a).

Next, we conducted contribution analyses to test whether the significant findings truly represent coherence among most experiments or are merely driven by a few experiments. For each significant cluster, we computed the fraction of the ALE value (the sum

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**Fig. 1 | ANM technique.**

- **a.** Four-millimetre spheres centred on peak coordinates reported in each experiment were created and combined to obtain combined activation seed. Then, for each of the 1,000 subjects in the normative human connectome, a subject-level seed-based functional connectivity map was computed and transformed to a Fisher \( z \) map. **b.** For the ‘overlap approach’, the above 1,000 subject-level Fisher \( z \) maps for each experiment were compared against zero using a voxelwise one-sample \( t \)-test with a threshold of \( T > 5.23 \) (corresponding to a voxelwise FWE-corrected \( P < 0.05 \)). **c.** The resulting thresholded experiment-level \( t \) maps were binarized and overlapped, then thresholded at 60% to identify regions functionally connected to more than 60% of the activation seeds. **d.** For the complementary ‘\( t \)-test’ approach, the above 1,000 subject-level Fisher \( z \) maps of each experiment in **a** were averaged to create an experiment-level mean Fisher \( z \) map. **e.** These experiment-level mean Fisher \( z \) maps were compared against zero using a one-sample \( t \)-test to identify brain regions significantly connected to brain activations across experiments.
of the ALE value of all voxels) that was accounted for by each experiment. If the fraction of an experiment is higher than the mean of the total ALE value, it will be deemed as contributing to that cluster. The results of contribution analysis indicate that only 21% of experiments in anger (8/39), 29% of experiments in disgust (7/24), 37% of experiments in happiness (11/44), 25% of experiments in fear (29/78), 17% of experiments in sadness (4/23) contributed to their most consistent findings respectively. Although with large sample sizes, the significantly activated regions were sparse for sadness, happiness and disgust. Such low reproducibility is unlikely to be driven by the heterogeneous experimental paradigm across experiments, since the reproducibility is still poor when ALE analyses were conducted on experiments grouped by paradigm rather than emotion type, with only 23% (11/47) in ‘valence decision’ paradigm, 22% (16/72) in ‘gender decision’ paradigm and 22% (8/36) in ‘passive viewing’ paradigm contributing to their most consistent findings respectively (see Supplementary Methods 5 and Supplementary Fig. 2 for a detailed description of the methods and results).

Between emotions, no brain regions displayed consistent activation across all five basic emotions, and only the left amygdala showed activation in four of the five basic emotions. The spatial correlation matrix between each pair of unthresholded z maps obtained from the ALE meta-analysis illustrated low similarities in activation patterns among the basic emotions (mean spatial correlation $r = 0.21$, Supplementary Fig. 8).

Next, we performed ANM (Fig. 1) to determine whether these highly inconsistent brain activations across experiments localized to a common network. Utilizing a large resting-state normative connectome ($n = 1,000$), ANM derives the underlying brain network of certain cognitive processing based on brain activations obtained from task fMRI analysis. It treats brain activation as seed and computes its functional connectivity to every voxel in the whole brain using the seed-based resting-state functional connectivity (RSFC) technique, yielding a network map for the brain activations of each experiment. The resulting activation network overlap maps showed that, within each basic emotion, over 92% of activation seeds in anger (36/39), 88% of activation seeds in disgust (21/24), 81% of activation seeds in fear (63/78), 66% of activation seeds in happiness (29/44) and 78% of activation seeds in sadness (18/23) were functionally connected to the same region (Fig. 2b). Other basic emotions illustrated that the similarities of network patterns were very high, ranging from 0.77 to 0.87 (mean spatial correlation $r = 0.82$). These similarities were significantly higher than those determined by the ALE meta-analysis ($t_{(80)} = 34.91, P < 0.001, d = 15.61, 95\% CI 0.58–0.66$; Supplementary Fig. 8).

Similar results were found in activation network $t$ maps obtained using the complementary ‘t approach’, with the temporal pole also being the most significantly connected region and with considerable similarities of network patterns among the basic emotions (mean spatial correlation $r = 0.85$; Fig. 2c, Supplementary Table 4 and Supplementary Figs. 4, 7 and 8). No significant differences were found when contrasting the activation network $t$ map of each emotion with the remaining four emotions combined (Supplementary Methods 4).

The spatial correlations between the unthresholded network overlap map and unthresholded network $t$ map under each basic emotion ranged from 0.76 to 0.85 (mean spatial correlation $r = 0.82$), indicating that the resulting network maps were highly consistent across the two complementary approaches.

**ALE and ANM analyses of general emotion processing.** To identify the brain mechanisms of emotion-general expression processing, experiments of all emotions were pooled and analysed using the same approaches as above. Similar to the findings for individual basic emotions, ALE analysis of emotion-general expression processing revealed that the significantly activated regions were sparse (Fig. 3a). The contribution analysis revealed that the most convergent cluster was contributed by only 19% (44/230) of experiments. In contrast, the ANM analysis of the same experiments showed that these heterogeneous activations are commonly connected to the same set of brain regions, with 73% (169/230) of activation seeds connecting to the most convergent cluster (Fig. 3c and Supplementary Fig. 5). The difference of reproducibility between ALE and ANM results persists even when the number of suprathreshold voxels was deliberately matched between these two types of maps (Fig. 3d,e). In particular, for the modelled activation overlap map, only one cluster in the right thalamus and insula was ‘activated’ in more than 60% of experiments. None of the 13 TMS stimulation seeds that disrupt facial emotion processing intersected the modelled activation overlap map, while 9 of them intersected the activation network overlap map (Supplementary Fig. 14). The activation network $t$ map included well-known emotion-related regions such as the orbitofrontal cortex, insula, amygdala, hypothalamus, cingulate gyrus, hippocampus and many other subcortical nuclei (Fig. 3b). Moreover, the visual cortex, which includes the fusiform face area, is also part of the identified facial emotion processing network. Since the network patterns among basic emotions are highly similar, these results are unlikely to be driven by any single type of emotion. The conjunction between the activation network map and its specificity map showed that connectivity to these regions was mainly specific compared with brain activations during non-emotional cognitive processing (Fig. 3d,f).

Since the resulting activation network overlap map and $t$ map of emotion-general expression processing are very similar (spatial correlation of 0.85; Fig. 3c,d and Supplementary Fig. 5), to make full use of the high statistical power afforded by the large sample size ($n = 230$) and to avoid arbitrariness when setting the experiment-level and group-level threshold in the ‘overlap’ approach, we decided to focus on the activation network $t$ map in the following robustness and validation analyses.

The network pattern of emotion-general expression processing was highly reliable when split into two randomized subgroups (spatial correlation $r = 0.90$, Supplementary Fig. 9), when the connectome dataset was preprocessed with high-pass filtering (spatial correlation $r = 0.91$, Supplementary Fig. 10a), when a larger seed size of 8 mm was used (spatial correlation $r = 0.99$, Supplementary Fig. 10b) or when another independent normative connectome dataset (Genome Superstruct Project, GSP) was used (spatial correlation $r = 0.88$, Supplementary Fig. 10c). When the analysis was

| Table 1 | Descriptive statistics of the emotions included in the meta-analyses |
|---------|------------------|--------|---|---|---|
| Emotion | Studies | Experiments | Participants | Foci |
| Anger | 37 | 39 | 1,226 | 224 |
| Aversion | 2 | 2 | 88 | 16 |
| Disgust | 24 | 24 | 415 | 202 |
| Fear | 75 | 78 | 1,799 | 620 |
| Happiness | 43 | 44 | 1,156 | 362 |
| Approach | 2 | 2 | 29 | 17 |
| Negative | 11 | 11 | 236 | 102 |
| Pain | 3 | 3 | 40 | 83 |
| Sadness | 22 | 23 | 741 | 179 |
| Surprise | 4 | 4 | 67 | 29 |
repeated with each coordinate as an individual seed, a similar network pattern was still observed (spatial correlation \( r = 0.95 \)), and the significant regions identified using the ‘combined seed’ were still clearly present in networks derived using the ‘uncombined seed’ (Supplementary Fig. 11). Additional ANM analysis that balanced the number of experiments across basic emotions indicated that our results were not biased by the unequal number of experiments across different emotions (spatial correlation \( r = 0.99 \), Supplementary Fig. 12). When the ANM analysis was repeated using meta-analytic coactivation modelling (MACM) to derive the functional connectivity network instead, the resulting network was roughly consistent with that obtained using RSFC, with most of the regions identified using MACM overlapping with that using RSFC (Supplementary Fig. 13).

**Relevance to TMS sites disrupting facial emotion processing.** We examined TMS studies on facial emotion processing to test whether the network derived from ANM aligned with the results of prior brain stimulation studies. Through a systematic literature search, we identified 9 studies with 13 stimulation sites that disrupt facial emotion processing in healthy subjects (Supplementary Table 2 and Supplementary Fig. 15). Like brain activations during facial emotion processing, stimulation sites reported to disrupt facial emotion processing have been highly heterogeneous across different studies. However, 11 of the 13 stimulation seeds overlapped with the facial emotion processing network derived from ANM. The remaining two seeds were within 3 mm and 6 mm of the nearest cluster, respectively (Fig. 4a), possibly because of registration error during image preprocessing, partial volume effects, etc. Nine of the 13 stimulation seeds overlapped with the emotion-specific network obtained from specificity analysis.

Network localization of heterogeneous TMS stimulation sites using the ANM technique indicated that these different stimulation sites were also part of a common functionally connected brain network, and this network is very similar to our facial emotion networks derived from brain activations (spatial correlation \( r = 0.74 \), Fig. 4a,b).

Region of interest (ROI)-based sensitivity and specificity analyses indicated that stimulation sites that disrupt facial emotion processing were significantly connected to activations of facial emotion processing (\( t_{229} = 12.84, P < 0.001, d = 0.85, 95\% \text{ CI } 0.13–0.18 \)) and that this connectivity was specific when compared with activations of both non-emotional cognitive processing (\( t_{487} = 4.87, P < 0.001, d = 0.52, 95\% \text{ CI } 0.06–0.14 \)) and vertex control sites (\( t_{458} = 9.65, P < 0.001, d = 0.90, 95\% \text{ CI } 0.11–0.17; \text{Fig. } 4c \)).

**Relevance to gray matter volume (GMV) reduction in alexithymia.** Four peak coordinates were reported in Xu’s study. Three of the four spherical seeds centred on these coordinates overlapped with our localized facial emotion processing network. The remaining site was within 4 mm of the nearest cluster, possibly due to registration error during image preprocessing, or partial volume effects as above. Two spherical seeds overlapped with the emotion-specific network derived from specificity analysis. ROI-based sensitivity and specificity analyses showed that brain activations under facial emotion processing were significantly connected to brain regions associated with alexithymia (\( t_{552} = 3.10, P = 0.002, d = 0.20, 95\% \text{ CI } 0.01–0.03 \)). This connectivity was specific to brain activations.
Fig. 3 | ALE and ANM results of emotion-general expression processing. **a**, ALE meta-analysis of emotion-general expression processing, revealing that the significantly activated regions were sparse. Furthermore, contribution analysis revealed that the most convergent cluster was contributed by only 19% of experiments, indicating the low reproducibility of activations across studies. To be consistent with ANM analyses, voxelwise FWE-corrected $P < 0.05$ was used for multiple comparison correction. **b**, The modelled activation overlap map. When the number of suprathreshold voxels was deliberately balanced between ALE and ANM maps, the reproducibility indicated was still lower than that shown by the activation network overlap map, with only one major cluster found to be ‘activated’ in more than 60% of experiments. **c**, The activation network overlap map, showing regions functionally connected to more than 60% of activation seeds. **d**, The specificity of the activation network overlap map, evaluated by comparing the binarized experiment-level $t$ map with that of non-emotional control experiments. The conjunction (yellow) between the activation network overlap map (red) and its specificity map (blue) indicated that a large part of the localized network was specific to facial emotion processing. **e**, The pattern of the activation network $t$ map, which is similar to that of the activation network overlap map. **f**, The specificity of the activation network $t$ map (blue) evaluated by comparing the experiment-level mean Fisher $z$ map with that of non-emotional control experiments. The conjunction between these two maps indicated that a large part of the localized network was specific to facial emotion processing. Emo, emotional; Non-emo, non-emotional. The values under each map are coordinates.
during facial emotion processing when compared with non-emotional cognitive processing ($t_{373} = 3.83$, $P < 0.001$, $d = 0.41$, 95% CI 0.02–0.06; Fig. 5).

**Relevance to lesions that disrupt facial emotion processing.** Both the insula and ventromedial prefrontal cortex (vmPFC) partly overlapped with the identified facial emotion processing network, whereas the entire bilateral amygdala was included within this network. ROI-based sensitivity and specificity analyses showed that all three regions were significantly connected to brain activations during facial emotion processing (amygdala: $t_{229} = 9.66$, $P < 0.001$, $d = 0.64$, 95% CI 0.10–0.16; insula: $t_{229} = 4.17$, $P < 0.001$, $d = 0.28$, 95% CI 0.04–0.10; vmPFC: $t_{229} = 2.39$, $P = 0.02$, $d = 0.16$, 95% CI 0.01–0.08). All these connectivities were specific compared with control brain lesion (amygdala: $t_{458} = 12.06$, $P < 0.001$, $d = 1.13$, 95% CI 0.20–0.28; insula: $t_{458} = 8.05$, $P < 0.001$, $d = 0.75$, 95% CI 0.13–0.22; vmPFC: $t_{458} = 6.52$, $P < 0.001$, $d = 0.61$, 95% CI 0.10–0.19). For the amygdala and vmPFC, but not the insula, these connectivities were also specific compared with non-emotional cognitive processing (amygdala: $t_{373} = 5.67$, $P < 0.001$, $d = 0.60$, 95% CI 0.07–0.15; insula: $t_{373} = -1.97$, $P = 0.05$, $d = -0.21$, 95% CI −0.11 to −0.00; vmPFC: $t_{373} = 3.54$, $P < 0.001$, $d = 0.38$, 95% CI 0.05–0.16; Fig. 6).

**Generalizability of ANM beyond facial emotion processing.** To test whether ANM can be generalized to localize networks of other cognitive processes, we applied this technique to rumination, a self-referential processing that is widely believed to be conceptualized by default mode network (DMN).
Finally, we validate the generalizability of ANM by using it to localize the network of rumination.

Our study is the first to empirically show that network localization could, at least partly, explain the low reproducibility observed across functional neuroimaging studies and that these heterogeneous brain locations activated during facial emotion processing localize to a common connected brain network. The latter is consistent with findings from previous LNM studies that showed that heterogeneous brain lesions localize to a common network across a variety of neurologic and neuropsychiatric symptoms as well as neurodegenerative diseases. However, it is worth noting that the current work only suggests that localizing brain function to discrete brain regions rather than networks may be one of the main reasons for the low reproducibility that commonly exists in functional imaging studies, but not the only reason.

Factors contributing to low reproducibility can be categorized into two groups. The first is the 'false-positive' group. This group can lead to activations of brain regions that are not associated with the target brain function, for example, the noise signal and flexible implementation of experimental procedures. This group could reduce the reproducibility of both traditional activation localization studies and our network localization and bias us towards finding regions that are not specific to emotion. This may explain why we did not find brain regions that were connected to all activation seeds.

The second group is termed 'false negative'. This group can make brain regions associated with target cognitive function undetectable. For example, in studies with low statistical power due to small sample size, only the strongly activated neural components (such as hub regions) of the network could survive the statistical threshold, leading weakly activated regions undetected. Furthermore, cognitive functions emerge from combinations of basic psychological and neural units. Different neuroimaging studies investigating the same cognitive function may use different types of experimental materials and tasks, which may have different demands on the same psychological unit, thus the differential likelihood of activation on the same neural unit.

With the ANM technique, we can take advantage of the high statistical power guaranteed by the large resting-state normative human connectome (1,000 subjects) to recover the undetected brain components of the network, thus greatly reducing the effect of false-negative factors and boosting reproducibility across different studies. To mitigate false positives and obtain a more emotion-specific network, we contrasted activation network maps of facial emotion processing with those of non-emotional control processes. Still, further refinement is possible.

To localize the network of facial emotion processing, we used two complementary approaches: the 'overlap' approach and the 't-test' approach. The 'overlap' approach was adopted from previous LNM studies. It has the following advantages when compared with the 't-test' approach: (1) The experiment-level binarized map could be interpreted straightforwardly (connected or not), just like a traditional binarized lesion map (lesioned or not). (2) Due to autocorrelation, voxels inside the seed region of the subject-level Fisher z map will have extremely high value, which may lead to biased value in seed region in the 't-test' approach. However, using the binarized map in the 'overlap' approach can avoid such bias. (3) By overlapping experiment-level binarized maps, we can avoid group-level results from being driven by extreme values in a small number of experiment-level maps, which makes the 'overlap percentage' an ideal measure of reproducibility. However, the 'overlap' approach also has some limitations: (1) As pointed out by Sperber and Dadashi, when testing the subject-level Fisher z maps against zero using one-sample t-test, the resulting experiment-level binarized t map is largely dependent upon the t-value threshold and sample size of the normative connectome, both of which lack clear guidelines and were somewhat arbitrary and inconsistent in LNM studies.

Fig. 5 | Relevance to structural abnormalities in alexithymia. Three of the four spheres centred on peak coordinates of structural abnormality in patients with alexithymia, a subclinical deficiency in the ability to identify and express emotions (green; only two representative spheres are shown), overlap with our localized network. Regions activated during facial emotion processing (n = 230) are functionally connected to brain regions in which grey matter volume is associated with alexithymia (one-sample t-test against zero mean, two-sided: t_{229} = 3.10, P = 0.002, d = 0.20, 95% CI 0.01–0.03). These connectivities are specific to regions activated during facial emotion processing (n = 230) compared with regions activated during non-emotional cognitive processing (n = 145) (two-sample t-test, two-sided: t_{230} = 3.83, P = 1.52 × 10^{-4}, d = 0.41, 95% CI 0.02–0.06). Boxplots indicate the 25th to 75th percentiles (coloured areas) and median (central lines). Whiskers represent the most extreme data points not considered outliers (minimum and maximum). Black circles show outliers (values more than q75 + 1.5 × (q75 – q25) or less than q25 – 1.5 × (q75 – q25)). *P < 0.05; **P < 0.01; ***P < 0.001. Emo, emotional; Non-emo, non-emotional.

task-based fMRI studies of rumination using the ALE technique revealed that the neuroimaging findings are heterogeneous, with only three small clusters found to be significantly involved in rumination (Fig. 7a). Subsequent contribution analysis also indicated that only 29–43% of experiments contribute to these clusters.

However, the network of rumination localized via ANM indicated that these seemingly inconsistent activations across neuroimaging studies were connected to a common set of brain regions (Fig. 7d). The difference of reproducibility between ALE and ANM results persisted even when the number of suprathreshold voxels was deliberately matched between these two types of maps, with only one cluster found to be ‘activating’ in more than 80% of experiments (Figs. 7b,d). The pattern of the network of rumination identified from ANM matches remarkably well with the DMN delineated by Yeo et al. Most of these commonly connected regions fall within classic DMN regions, such as the middle temporal cortex, posterior cingulate cortex, posteromedial cortex, angular gyrus and medial prefrontal cortex. The conjunction between the activation network overlap map of rumination and its specificity map indicated that our identified network was specific to rumination and cannot be obtained by randomly selected neuroimaging studies.

Discussion
Using the new ANM technique, we obtain several noteworthy results. First, though the results of discrete-brain-based ALE meta-analysis indicate that reproducibility is relatively low across neuroimaging findings, they are indeed highly reproducible in terms of connectivity and network. Second, the shared brain networks across five basic emotions support conceptual act theory rather than basic emotion theory. Third, our network localization of facial emotion processing aligns remarkably well with TMS stimulation sites, brain structural abnormalities and lesions associated with facial emotion processing.
When thresholding the group-level overlap map, the ‘percentage’ threshold was also arbitrary and inconsistent and lacks guidelines across previous LNM studies (ranging from 55% to 93%)\textsuperscript{11,30,36}. To overcome these limitations, we proposed the ‘t-test’ approach, in which the experiment-level statistical thresholding was avoided. Specifically, instead of testing these 1,000 subject-level Fisher z maps against zero via t-test, we averaged these 1,000 subject-level Fisher z maps to obtain an experiment-level mean Fisher z map. Then, we tested these experiment-level mean Fisher z maps against zero by resorting to common practice in statistical parametric mapping.

Our ANM analysis revealed a complex and interconnected network involved in facial emotion processing. This network includes

![Diagram of brain regions with correlation values and significance levels]

**Fig. 6 | Relevance to lesions that disrupt facial emotion processing.** Lesions in the amygdala, insula and vmPFC have reliably been demonstrated to disrupt a person’s ability to recognize emotional facial expressions. All three ROIs (green) overlapped our localized network. ROI-based sensitivity and specificity analyses also showed that regions activated during facial emotion processing (n = 230) were functionally connected to the amygdala (one-sample t-test against zero mean, two-sided: $t_{229} = 9.66$, $P = 9.85 \times 10^{-15}$, uncorrected, $d = 0.64$, 95% CI 0.10–0.16), insula (one-sample t-test against zero mean, two-sided: $t_{229} = 4.17$, $P = 4.25 \times 10^{-5}$, uncorrected, $d = 0.28$, 95% CI 0.04–0.10) and vmPFC (one-sample t-test against zero mean, two-sided: $t_{229} = 2.39$, $P = 0.02$, uncorrected, $d = 0.16$, 95% CI 0.01–0.08). All these connectivities were specific compared with control brain lesion (two-sample t-test, two-sided $P$ value, uncorrected; amygdala: $t_{458} = 12.06$, $P = 2.71 \times 10^{-29}$, $d = 1.13$, 95% CI 0.20–0.28; insula: $t_{458} = 8.05$, $P = 7.07 \times 10^{-15}$, $d = 0.75$, 95% CI 0.13–0.22; vmPFC: $t_{458} = 6.52$, $P = 1.81 \times 10^{-13}$, $d = 0.61$, 95% CI 0.10–0.19). For the amygdala and vmPFC, these connectivities were specific to regions activated during facial emotion processing (n = 230) compared with regions activated during non-emotional cognitive processing (n = 145) (two-sample t-test, two-sided $P$ value, uncorrected; amygdala: $t_{373} = 5.67$, $P = 2.90 \times 10^{-6}$, $d = 0.60$, 95% CI 0.07–0.15; insula: $t_{373} = 1.97$, $P = 0.05$, $d = -0.21$, 95% CI $-0.11$ to $-0.00$; vmPFC: $t_{373} = 3.54$, $P = 4.57 \times 10^{-4}$, $d = 0.38$, 95% CI 0.05–0.16). Boxplots indicate the 25th to 75th percentiles (coloured areas) and median (central lines). Whiskers represent the most extreme data points not considered outliers (minimum and maximum). Black circles show outliers (values more than $q_{75} + 1.5 \times (q_{75} - q_{25})$ or less than $q_{25} - 1.5 \times (q_{75} - q_{25})$. *$P < 0.05$; ***$P < 0.001$. The dashed horizontal lines indicate zero on the y-axis; NS, not statistically significant. Emo, emotional; Non-emo, non-emotional.
well-known emotion-related regions such as the amygdala\textsuperscript{37}, insula\textsuperscript{38}, medial prefrontal cortex\textsuperscript{39} and thalamus\textsuperscript{40}. Although neutral faces were used as control stimuli in the original task-fMRI experiments, this network also comprises a large part of the visual cortex that includes the fusiform face area. This is consistent with previous findings that visual cortical activity and emotion are intertwined\textsuperscript{41}. Both activation network overlap maps and activation network \( t \) maps indicate that the temporal pole is the most connected region for all five basic emotions as well as the emotion-general category. The temporal pole has long been considered part of the extended limbic system due to its tight connections with the limbic and paralimbic systems\textsuperscript{42}. By binding highly processed perceptual information to visceral emotional responses, it takes part in both social and emotional processing, including facial recognition\textsuperscript{43} and theory of mind\textsuperscript{44} (see ref. \textsuperscript{45} for a review).

Though the low similarity between activation patterns of basic emotions from activation-based ALE meta-analysis seems to support basic emotion theory, our results from network-based ANM

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**Fig. 7** Heterogeneous neuroimaging findings of rumination are part of a common network.  

**a**, ALE analysis of functional neuroimaging findings of rumination, indicating that the significantly activated regions were sparse. Contribution analysis revealed that these convergent regions were contributed by only 29–43% of experiments. **b**, When the number of suprathreshold voxels was deliberately balanced between the ALE map (modelled activation map) and the ANM map, the reproducibility indicated by the modelled activation overlap map was still lower than that of the activation network overlap map, with only one major cluster found to be ‘activated’ in more than 80% of experiments. **c, d**, Comparison of the DMN defined by Yeo et al.\textsuperscript{28} (c) with the ANM map of the rumination circuit (d). ANM analysis of these heterogeneous neuroimaging findings of rumination revealed that they are connected to a common network. All 14 heterogeneous activation seeds fell within or overlapped with the identified network. This network matched very well with the DMN, a well-defined network that is widely accepted as the neural conceptualization of rumination. A more stringent overlap threshold of 80% was used here. **e**, Specificity of the activation network overlap map of rumination evaluated by contrasting with control experiments (\( n = 200 \)) randomly selected from the BrainMap database. Red represents the activation network overlap map of rumination, blue is its specificity map and yellow is the overlap. The values under each map are coordinates.
meta-analysis indicate that different basic emotions share a common set of neural components. In line with prior work, we found that common brain regions such as the amygdala, insula, medial prefrontal cortex and visual cortex are consistently connected across different basic emotions. These findings provide strong evidence for conceptual act theory, which proposes that emotions arise from the combination of emotion-general or even domain-general basic cognitive (and corresponding neural components) that perform basic cognitive functions such as sensation, attention and memory.

Another interesting finding is that ALE analysis indicated that the middle occipital gyrus was the sole region significantly activated in disgust, making it distinct from all other emotions, whereas ANM analysis showed that the network pattern for disgust was highly similar to that of other emotions, with the temporal pole, fusiform gyrus, amygdala and insula being the most connected regions. All these results imply that exploring brain–behaviour relations at different levels (either the level of individual brain regions or the level of the network) could sometimes lead to entirely different results. In most cases, understanding brain–behaviour mappings at the level of individual brain regions is less productive since complex behaviours are always collectively supported by networks of brain regions.

We found that both the amygdala and vmPFC were specifically connected to emotion-related activations. The vmPFC is reciprocally connected to the amygdala and plays an important role in emotion regulation. It is also an important part of the DMN, which is an intrinsic network specialized for internally oriented cognitive processes and shows decreased activity during performance of experimental tasks. This may explain the observed negative connections between the vmPFC and brain activations of non-emotional cognitive processing. Of note, although the insula was significantly connected to facial emotion processing–related activations, these connections were not specific compared with non-emotional cognitive processing. This is not surprising, given that the insula is involved in a wide variety of cognitive processes such as perception, attention, memory and language and has extensive reciprocal connections with frontal, temporal, parietal, occipital lobes and limbic areas.

Functional neuroimaging research has long been criticized for providing only correlational but not necessarily causal information. However, our network derived from ANM aligned remarkably well with the network derived from heterogeneous TMS stimulation sites that disrupt facial emotion processing in healthy individuals, and a causal relationship between brain and behaviour can be drawn from TMS studies. Nevertheless, future work can address whether our network can differentiate TMS stimulation sites that disrupt facial emotion from those that do not. Our ANM results are also consistent with the results of voxel-based morphometry (VBM) studies of alexithymia and lesion–behaviour studies (as the gold standard) of facial emotion processing. Qualitatively, these structurally abnormal regions and lesions overlap with our localized network. Quantitatively, they are functionally connected to brain activations during facial emotion processing. Although a few of the peaks in TMS and VBM studies fall outside of our identified facial emotion network, they were found to be very close to this network, which means it is unlikely that these peaks represent significant brain regions that were missed by our localized network. This further proved that the relationship between brain networks derived from ANM and facial emotion processing is not correlational but causal. Convergent findings of these four tools (functional neuroimaging, VBM, TMS and lesions) make us confident in the validity of ANM as a new tool to localize networks of cognitive functions in healthy individuals. It also adds new connectivity-based evidence to the theory of ‘coupling between the structure and function of the human brain’.

There are several limitations to our study. First, as with previous coordinate-based network mapping studies, we created spheres centred on each coordinate and combined them to model the activation map of functional neuroimaging studies. However, the real activation map may have continuously extended broadly across brain regions, thus a large proportion of activating signals could have been missed in the activation seeds. A potential solution to this limitation would be to extract ROIs from activation-based or connectivity-based parcellation atlases (for example, the Atlas of Intrinsic Connectivity of Homotopic Areas) that reported activation coordinates fall within, and use these ROIs as seeds. Second, unlike previous LNM studies, we did not find brain regions that were connected to 100% of the activation seeds, and in some cases, we also used a less conservative overlapping threshold (60%). In other words, the reproducibility of the network localized by the ANM technique seems to be lower than that localized by LNM. This occurrence is reasonable to expect, given that, compared with brain lesions, brain activations are temporarily unstable, more vulnerable to methodological heterogeneity and hampered by noises abundant in functional neuroimaging. All these factors can introduce noise into our ANM results. However, they should bias us against finding the present common brain network. Third, the present study was limited to only two psychological functions (facial emotion processing and rumination). To extend the validity of this technique, it will be necessary to use it to localize networks of more psychological functions. Like facial emotion processing and rumination, many other psychological functions, such as vision, memory, language, attention and social cognition, have been shown to emerge from a distributed set of brain regions interacting with each other to form a network. Therefore, we are optimistic that this technique can also be used to localize networks of these psychological functions.

Methods
This work did not involve the collection of new data and was limited to analyzing existing results from a meta-analysis of the published literature. As such, no ethics board approval was obtained. No statistical methods were used to predetermine sample sizes, but our sample size is greater than that in most previous comparable studies. The resolution of all analyses is 2 mm unless otherwise noted, and all statistical tests were performed using two-tailed t-tests.

Study selection. We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (http://www.prisma-statement.org) to identify functional neuroimaging studies of facial emotion processing. Studies published from 1 November 1992 to 14 June 2018 were identified by a literature search of PubMed using the following combination of search terms: (emotion OR affect OR happy’ OR ‘angry’ OR ‘fear’ OR ‘sad’ OR ‘disgust’ OR ‘valence’ OR ‘pleasant’ OR ‘unpleasant’) AND (‘face’ OR ‘facial’ OR ‘expression’) AND (‘fMRI’ OR ‘functional MRI’ OR ‘functional magnetic resonance imaging’ OR ‘PET OR ‘positron emission tomography’ OR ‘neuroimaging’). Other sources included reference lists of previous emotion-related meta-analytic studies, review articles and finally selected studies. Since there are many cases where a single study contains multiple candidate experiments (each experiment corresponds to a contrast), we based our analysis on experiment rather than study. We only included experiments that (1) made use of IMRI or positron-emission tomography, (2) involved healthy adult participants, (3) used emotional facial stimuli that could be categorized into one type of emotion, (4) reported whole-brain results in Talairach or MNI space, (5) included activation coordinates (not deactivation) and (6) used neutral faces as control stimuli to ensure that the reported activation coordinates are exclusively emotion related and do not include face-related components.

To obtain a comprehensive and representative control group, we selected non-emotional cognitive processing experiments from the BrainMap database. As of October 2020, BrainMap included more than 130,000 experiments. These experiments were categorized into five behaviour domains: action, cognition, emotion, perception and interoception. To be consistent with the inclusion criteria of the facial emotion processing experiments described above, we only included experiments that (1) made use of IMRI or positron-emission tomography, (2) involved healthy adult participants, (3) reported whole-brain results in Talairach or MNI space, (4) reported activation data (not deactivation) and (5) belonged to behaviour domains other than emotion. Finally, 145 non-emotional experiments were randomly selected from candidate experiments that met all these inclusion criteria (Supplementary Table 5).

ALE. Activation-based meta-analysis was performed using GingerALE 2.3.6 (http://www.brainmap.org/ale). A detailed description of the ALE algorithm has been published elsewhere. Briefly, coordinates reported in Talairach space
were linearly transformed into MNI space using the Lancaster transformation. The modelled activation map for each experiment was created by modelling each coordinate within each experiment as the centre of a three-dimensional Gaussian kernel with a full-width at half-maximum (FWHM) of 6 mm, the threshold size and probabilities of activation in each voxel. To identify clusters of significant convergence, these modelled activation maps were compared with those from a null distribution by relocating the same number of foci randomly across the whole brain. This comparison resulted in non-parametric \( P \)-value maps that were further thresholded at \( P < 0.05 \), cluster-level corrected (with a cluster-forming threshold at voxel-level \( P < 0.001 \)) with 1,000 permutations to correct for multiple comparisons.

To test whether the significant findings truly represent coherence among most experiments or are merely driven by a small part of them, we performed contribution analysis using the tool implemented in GingerALE 2.3.6. This tool computes the number of experiments that contribute to each statistically significant activation cluster obtained after ALE analysis (see Supplementary Methods 3 for a detailed description of the algorithm).

ANM. To test whether brain activations associated with facial emotion processing localized to a common network, we used a new technique termed ANM, which was extended from the LNMS technique. First, a 4-mm-radius sphere centred on each coordinate of an experiment was created. To allow experiment-level random-effect inferences, we merged these spheres of the same experiment to obtain a combined seed (hereafter called ‘activation seed’). Then, using RSFC based on a normative connectome (www.lead-dbs.org) of 1,000 subjects from the Human Connectome Project (HCP) (Supplementary Methods 11) to identify activated voxels defined as brain regions functionally connected to the activation seed. Specifically, for each normative subject in our HCP dataset, we calculated Pearson’s correlation coefficient between the average time course of all voxels within the activation seed and the time course of every voxel in the whole brain. Each of the resulting 1,000 subject-level \( r \)-maps was transformed to a Fisher z-map via Fisher’s z transformation. Next, we conducted a complementary sensitivity analysis to obtain a brain-level activation network map (Fig. 1). In the first approach (the ‘overlap’ approach), the above 1,000 subject-level Fisher z-maps for each experiment were compared against zero using a voxelwise one-sample \( t \)-test. Each of the resulting experiment-level \( t \)-maps was then thresholded and binarized at \( T > 5.23 \) (corresponding to voxelwise familywise error (FWE)-corrected \( P < 0.001 \)). Finally, all binarized maps were overlapped and thresholded at 60% to create a group-level activation network overlap map. The suprathreshold clusters in this map were brain regions functionally connected to more than 60% of activation seeds.

In the second approach (the ‘t-test’ approach), the above 1,000 subject-level Fisher z-maps of each experiment were averaged to create an experiment-level mean Fisher z-map. Then, these experiment-level mean Fisher z maps that belong to the same group (for example, the same emotion category) were compared against zero using a voxelwise one-sample \( t \)-test, with multiple comparisons corrected at cluster-level FWE \( P < 0.05 \) (cluster-forming threshold at voxel-level \( P < 0.001 \)) via non-parametric permutation tests implemented in Statistical Non-Parametric Mapping (SnPM13, http://warwick.ac.uk/snpm, 5,000 permutations). For groups of more than 100 experiments, the group-level \( t \)-map was thresholded at a more conservative \( T > 5.23 \) (corresponding to voxelwise FWE-corrected \( P < 0.05 \)) as above. The suprathreshold clusters were brain regions significantly connected to activation seeds across experiments.

Specificity of ANM. To control the possibility that the same network could also be identified by any set of experiments randomly selected from other cognitive processes and to test whether the obtained activation network maps were specific to facial emotion processing, we contrasted the identified activation network map of facial emotion processing with that of non-emotional cognitive processing. Specifically, for the activation network overlap map obtained via the ‘overlap’ approach, we compared the above experiment-level binarized activation network \( t \)-maps with those of non-emotional cognitive processing using non-parametric voxel-lesion symptom mapping (https://aphasialab.org/vlsm/). As recommended previously, only voxels that survived in more than 10% of our binarized activation network maps were included in the statistical analysis. For the activation network \( t \)-map obtained via the ‘t-test’ approach, we compared unthresholded activation network maps (experiment-level mean Fisher z-maps) of facial emotion processing with those of non-emotional cognitive processing using a voxelwise non-parametric two-sample \( t \)-test implemented in SnPM13. For both the ‘overlap’ and the ‘t-test’ approaches, we corrected multiple comparisons using permutation-based testing with 5,000 permutations and cluster-level FWE-corrected \( P < 0.05 \) (cluster-forming threshold at voxel-level \( P < 0.001 \)).

Robustness analyses. Multiple control analyses were conducted to test the robustness of the results:

- When comparing the reproducibility between ALE results and ANM results, we made an additional, more balanced comparison, in which we deliberately matched the percentage of suprathreshold voxels in each ALE map (modelled activation map) to the ANM map of the same experiment. Specifically, for each experiment-level thresholded ANM map, we calculated the percentage of suprathreshold voxels. Then, we used this percentage to threshold the modelled activation map of the same experiment. In this way, we can guarantee that both the thresholded ANM and modelled activation map of the same experiment have the same number of suprathreshold voxels. After that, like the above ‘overlap’ approximately valused forth modelled activation maps were binarized and overlapped, then further thresholded at 60%. The suprathreshold clusters in the group-level modelled activation overlap map can be viewed as brain regions that are consistently ‘activated’ in more than 60% of the experiments.
- Given the ongoing debate about whether the higher frequency signals are driven by the larger part of them, we performed ALE analysis (see Supplementary Methods 3 for a detailed description of the algorithm).
- To test whether our results were independent of the normative connectome database used to derive activation network maps, we repeated our ANM procedure using 1,000 normative connectomes of healthy subjects from another publicly available database (the ‘GSP’). The preprocessing steps of the GSP dataset are described in Supplementary Methods 2.
- To ensure that our network localization was independent of seed size, we repeated the analysis using a larger sphere size of 8 mm.
- To test for the internal reliability of our ANM results, we randomly divided facial emotion processing experiments under each emotion into two equal subgroups. Then, activation network maps were created separately for each subgroup as described above, and spatial correlation was computed to assess the similarity between these two maps.
- To validate the obtained network was not driven by combining coordinates of the same experiment to form a combined seed, the analysis was repeated but with each coordinate treated as an independent seed (uncombined seed) rather than combining them. Then, the activation network \( t \)-map of emotion-general expression processing was identified using the ANM technique as above.
- To determine whether the localized network of emotion-general expression processing is biased by the unequal number of experiments across different emotions, we repeated the analysis but with the same number of experiments (\( N = 23 \), as this is the lowest number of experiments included in these emotions) randomly selected from each basic emotion and pooled together.
- In our ANM analysis, we used task-independent RSFC to derive the functional connectivity network of each activation seed. Another commonly used method to derive seed-based connectivity networks is task-dependent MACM (see the review by Laird et al. for a detailed comparison between RSFC and MACM). To test whether the ANM technique is robust to different connectivity modelling methods, we conducted additional ANM analysis based on MACM (see Supplementary Methods 6 for a detailed description).

Relevance to TMS sites disrupting facial emotion processing. To identify studies in which facial emotion processing was disrupted by focal noninvasive brain stimulation using TMS, we searched PubMed for articles using the search terms (‘TMS’ OR ‘transcranial magnetic stimulation’) and (‘facial emotion’, OR ‘facial expression’, OR ‘affective’). A total of 372 studies were retrieved. We only included experiments that (1) involved healthy adult subjects, (2) used a facial emotion processing task, and reported disruption (either reduced accuracy or increased reaction time), (3) delivered TMS to the scalp covering the cerebral cortex and (4) listed stimulation coordinates in a standard reference space (Talairach or MNI). Stimulation coordinates were extracted from the selected studies, and a stimulation-site network overlap map was generated using the ANM procedures described above. We did not calculate the activation network \( t \)-map because of the low statistical power caused by the small sample size (\( n = 13 \)).

To test whether stimulation sites disrupting facial emotion processing were functionally connected with brain activation during facial emotion processing and whether such connectivity was specific, we conducted ROI-based sensitivity and specificity analyses. Briefly, a combined stimulation seed was created by combining all spherical seeds of stimulation sites as described above. We also created a combined control seed using vertex coordinates extracted from finally selected TMS sites studies since all these studies used vertices as control sites. As described above, for each of the 1,000 normative subjects in our HCP dataset, we calculated Pearson’s correlation coefficient between the average time course of voxels within the activation seed and that within the control seed. Then, spatial correlation was computed using the experimental-level \( z \)-score. Finally, group comparisons were analysed using a one-sample \( t \)-test for sensitivity analysis and a two-sample \( t \)-test for specificity analysis. We conducted ROI-based specificity analyses in two ways. First, we tested whether TMS stimulation sites disrupting facial emotion processing were significantly more connected to activation seeds of facial emotion processing than to activation seeds of non-emotional cognitive processing. Second, we tested whether TMS stimulation sites disrupting facial emotion processing were significantly more connected to activation seed of facial emotion processing than to vertex control seed.

Relevance to GMV reduction in alexithymia. Alexithymia refers to a deficiency in the ability to identify and express emotions. A recent meta-analytic VBM study of alexithymia by Xu et al. found converging brain regions with smaller
GMV in alexithymia. Peak coordinates of brain regions with converging GMV reduction were extracted from this meta-analysis. As described above, we created 4-mm spherical seeds centred on each coordinate and combined these seeds to create an atrophy seed of alexithymia. Then, ROI-based sensitivity and specificity analyses were conducted to test whether the atrophy seed of alexithymia was functionally connected to activation seeds of facial emotion processing and whether this connectivity was specific when compared with non-emotional cognitive processing.

Relevance to lesions that disrupt facial emotion processing. Previous focal lesion studies have reliably demonstrated that lesions in the amygdala, vmPFC, and insula disrupt a patient’s ability to recognize emotional facial expressions. To test whether these brain regions are functionally connected to brain activations during facial emotion processing and whether these functional connectivities are specific, ROI-based sensitivity and specificity analyses were performed as above. We used the lesions in dorsoventral prefrontal cortex as a control because considerable empirical evidence indicates that such lesions interrupt the performance of working memory but not facial emotion processing63,64. Unlike previous lesion networking mapping studies in which ROIs were typically derived from brain lesions of individual cases with documented impairments or symptoms, anatomical ROIs for the brain lesions in our study were defined according to Automated Anatomical Labelling template labels65.

Generalizability of ANM beyond facial emotion processing. To test whether ANM is also effective in localizing the brain network of other psychological processes, we chose rumination (a self-referential processing strongly associated with depression) based on the following factors: (1) functional neuroimaging findings of rumination are highly inconsistent79, (2) DMN is widely accepted as the network involved in self-attribution of an artificial hand: a lesion network-symptom-mapping. 8. Bressler, S. L. & Menon, V. Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn. Sci. 14, 277–290 (2010).
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Software and code

Policy information about availability of computer code

Data collection
- HCP and GSP normative connectome datasets were obtained from publicly available sources (www.humanconnectome.org for HCP and http://neuroinformatics.harvard.edu/gsp/ for GSP). No software were used for collection of these datasets.

Data analysis
- Data analysis was performed in MATLAB version 2017b (The MathWorks, Inc.) and through the following open source software packages: GingerALE 2.3.6 (http://www.brainmap.org/ale/), Neurosynth (https://github.com/neurosynth/neurosynth), HCP Functional Pipeline v2.0 (www.humanconnectome.org), GREtna (https://www.nitrc.org/projects/gretna), DPARSF (http://rfmri.org/DPARSF), SnPM13 (http://warwick.ac.uk/snpm), VLSM (https://aphasialab.org/vlsm/); Custom codes for Activation Network Mapping analysis are publicly available on GitHub (https://github.com/sailingpeng/2021_ActivationNetworkMapping.git).

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The normative connectome datasets are publicly available from the Human Connectome Project (HCP, https://www.humanconnectome.org) and the Genome Superstruct Project (GSP, https://dataverse.harvard.edu/dataverse/GSP); The coordinate information for facial emotion processing and non-emotional processing,
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- **Sample size**: Because there is no standard method for estimating sample size for this type of analysis, we attempted to identify as many studies as possible that explore the brain activation during facial emotion processing. Still, the sample size (N=230) in our study is greater than that in previous comparable studies.

- **Data exclusions**: We only include experiments that meet the following inclusion criteria: (i) made use of fMRI or PET; (ii) involved healthy adult participants; (iii) used emotional facial stimuli that could be categorized into one type of emotion; (iv) reported whole-brain results in Talairach or Montreal Neurological Institute (MNI) space; (v) included activation coordinates (not deactivation); (vi) used neutral faces as control stimuli. All these inclusion criteria were pre-established.

- **Replication**: We tested the internal consistency of the identified network of emotion-general expression processing by measuring its split-half reliability; we also used rigorous statistical techniques to test the robustness of the identified network of emotion-general expression processing using different seed size, different normative connectome dataset, different preprocessing strategy and different method of deriving seed-based functional connectivity. All replication attempts were successful.

- **Randomization**: This work was limited to the analysis of existing results from the published neuroimaging studies. As such, randomization was not applicable.

- **Blinding**: This work was limited to the analysis of existing results from the published neuroimaging studies. As such, blinding was not applicable.

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| [ ] | ChIP-seq |
| [ ] | Flow cytometry |
| [x] | MRI-based neuroimaging |

**Magnetic resonance imaging**

**Experimental design**

| Design type | Resting state |
|-------------|---------------|
| Design specifications | N/A |
| Behavioral performance measures | N/A |
**Acquisition**

| Imaging type(s)          | Functional images |
|--------------------------|-------------------|
| Field strength           | 3T                |
| Sequence & imaging parameters | Sequence and imaging parameters were described in original publications associated with all datasets. |
| Area of acquisition      | Whole brain       |
| Diffusion MRI            | Used              |
|                          | Not used          |

**Preprocessing**

| Preprocessing software    | DPARSF, GRETNA, and other preprocessing software described in original publications associated with all datasets. |
|---------------------------|----------------------------------------------------------------------------------------------------------------|
| Normalization             | Nonlinearly normalized to MNI space                                                                             |
| Normalization template    | MNI152                                                                                                          |
| Noise and artifact removal| Noise and artifact removal were described in original publications associated with all datasets.                |
| Volume censoring          | Data was not volume censored.                                                                                    |

**Statistical modeling & inference**

| Model type and settings   | No modelling was performed                                                                                      |
| Effect(s) tested          | Facial emotion processing versus non-emotional processing                                                      |
| Specify type of analysis  | □ Whole brain □ ROI-based □ Both                                                                                |
| Statistic type for inference | Both voxel-wise and cluster-wise inference were used. For cluster-wise inference, cluster-forming threshold at voxel-level $P < 0.001$ was adopted |
| Correction                | Different multiple comparison methods were used in different part of the study and are described in detail in the Method section |

**Models & analysis**

| n/a | Involved in the study |
|-----|-----------------------|
|     | □ Functional and/or effective connectivity |
|     | □ Graph analysis      |
|     | □ Multivariate modeling or predictive analysis |

| Functional and/or effective connectivity | Pearson correlation |