Activation Network Localization of Facial Emotion Processing

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Article

Keywords: facial emotion processing, activations, functional neuroimaging, connectivity, networks

DOI: https://doi.org/10.21203/rs.3.rs-279058/v1

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Abstract

Facial emotion processing is a basic psychological function of the human brain. Functional neuroimaging techniques have been widely used to probe its neural substrates in healthy subjects. However, like many other psychological functions, functional activations during facial emotion processing have been reported throughout the brain, and the findings are largely inconsistent across studies. Here, we attempted to test whether heterogeneous functional neuroimaging findings of facial emotion processing localized to a connected network and whether network localization could partly explain the poor reproducibility observed. First, using the activation likelihood estimation (ALE) meta-analysis technique, we showed that individual-brain-based reproducibility was low across studies. Then, using a new technique termed ‘activation network mapping’, which was adapted from lesion network mapping, we found that network-based reproducibility across these same studies was rather high; also, these seemingly heterogeneous functional neuroimaging findings mainly localized to a common brain network. Finally, our localized network based on activation matched brain stimulation locations—and the network derived from it—that disrupted facial emotion processing. It also aligned well with structural abnormalities in alexithymia—a disorder characterized by a deficiency in the ability to identify emotions, and brain lesions that disrupt facial emotion processing. Our results suggest that heterogeneous functional neuroimaging findings of facial emotion processing in healthy people localize to a common connected network, which improves the seemingly poor reproducibility among functional neuroimaging studies. Activation network mapping may prove to be a novel network-based technique that is potentially broadly applicable to localize brain networks of cognitive functions based on brain activations in healthy individuals.

Introduction

Facial emotion processing is a basic capacity of the human brain and plays a crucial role in normal social functioning. 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 factors such as variability in study design and subject characters; flexibility in data collection, analysis and reporting (Simmons, Nelson, & Simonsohn, 2011); and low statistical power (Ioannidis, 2005).

The prevailing definition of reproducibility in functional neuroimaging studies is mainly based on whether the same brain regions were activated (Eickhoff et al., 2009; Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011), ignoring connections between them. However, an increasing number of studies indicate that brain functions better localize to connected networks than to isolated brain regions (Bressler & Menon, 2010). Similar to the view of Darby, Joutsa, and Fox (2019), which states 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 and 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 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 (Boes et al., 2015; Darby, Joutsa, Burke, & Fox, 2018; Darby et al., 2019; Fasano, Laganiere, Lam, & Fox, 2017; Laganiere, Boes, & Fox, 2016). 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 (Burke et al., 2020; Tetreault et al., 2020; Weil, Hsu, Darby, Soussand, & Fox, 2019) and brain stimulation sites (Siddiqi et al., 2020) as seeds. Adapted from this technique, we proposed a novel technique termed activation network mapping (ANM) 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 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” (Cole, Ito, Bassett, & Schultz, 2016; Fries, 2005; V. A. Smith, Yu, Smulders, Hartemink, & Jarvis, 2006) and 2) resting-state network architecture highly resembles the task-evoked network architecture at both the individual subject level (Tavor et al., 2016) and group level (Cole, Bassett, Power, Braver, & Petersen, 2014; Crossley et al., 2013; Fair et al., 2007; Fox & Raichle, 2007; Greicius, Krasnow, Reiss, & Menon, 2003; S. M. Smith et al., 2009).

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 and whether the identified networks are composed of shared brain components between emotions. Second, we pooled experiments of all emotions together to localize an emotion-general face processing network and test its specificity by comparing it with the activation network of non-emotional cognitive processing. Third, we tested whether our localization of facial emotion processing aligned with transcranial magnetic stimulation (TMS) stimulation sites disrupting facial emotion processing. Finally, we tested whether these localizations align with structural abnormalities in alexithymia—a disorder characterized by a deficiency in the ability to identify emotions, and brain lesions causing facial emotion recognition disorder.

Methods

Study selection

We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org) to identify functional neuroimaging studies of facial
emotion processing. Studies published from November 1, 1992, to June 14, 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 include reference lists of previous emotion-related meta-analytic studies, review articles, and finally selected studies. We only included experiments that (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) used neutral faces as the control; (vi) included activation coordinates (not deactivation).

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 behavior domains—action, cognition, emotion, perception, and interoception. To be consistent with the inclusion criteria of facial emotion processing experiments described above, we only included experiments that (i) involved healthy adult participants; (ii) reported whole-brain results in Talairach or MNI space; (iii) reported activation data (not deactivation); (iv) belonged to behavior domains other than emotion. Finally, 145 non-emotional experiments were randomly selected from candidate experiments that met all these inclusion criteria.

**Activation likelihood estimation (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 (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Eickhoff et al., 2009). Briefly, coordinates reported in Talairach space were linearly transformed into MNI space using the Lancaster transformation (Lancaster et al., 2007). The modeled activation map for each experiment was created by modeling each coordinate within each experiment as the center of a three-dimensional Gaussian kernel with a full-width at half-maximum (FWHM) value corresponding to sample size and probabilities of activation in each voxel. To identify clusters of significant convergence, these modeled 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 nonparametric p-value maps that were further thresholded at P < 0.05, cluster-level corrected (cluster-forming threshold at voxel-level P < 0.001) with 1000 permutations to correct for multiple comparisons.

**ANM**

To test whether brain activations associated with facial emotion processing localize to a common network, we used a new technique termed ANM, which was extended from the LNM technique (Boes et al., 2015). First, a 4-mm sphere centered on each coordinate of an experiment was created. To allow experiment-level random-effect inferences (Eickhoff et al., 2009; Yarkoni et al., 2011), we merged these spheres of the same experiment to obtain a combined seed, which was treated as modeled activation maps. Then, using a normative connectome of 1000 subjects from the Human Connectome Project
(HCP) (Van Essen et al., 2013), we identified activation network maps defined as brain regions functionally connected to the modeled activation maps. 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 modeled activation map and the time course of every voxel in the whole brain. Each resulting subject-level r map was transformed to a z map via Fisher’s z transformation. We exclude negative correlations in our analysis since the interpretation of biological mechanisms of negative correlations is ambiguous (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). Next, we conducted two complementary types of sensitivity analyses to obtain a group-level activation network map (Fig. 1). In the first approach, the above 1000 subject-level z maps for each experiment were combined to generate an experiment-level t map using a voxelwise two-tailed one-sample t-test; the map was then thresholded and binarized at T > 5.23, corresponding to voxelwise familywise error (FWE)-corrected P < 0.05. Finally, all binarized maps within each emotion category overlapped and were 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 experiments. In the second approach, the above 1000 subject-level z maps of each experiment were averaged to create an experiment-level mean activation network z map. Then, all z maps under each emotion category were combined to create a group-level activation network t map using a voxelwise one-sample t-test. Finally, the resultant t map was thresholded at a cluster-level FWE corrected p-value of 0.05 (cluster-forming threshold at voxel-level p < 0.001). For the emotion-general category, the t map was thresholded at a more conservative voxel-level FWE corrected p-value of 0.05. The suprathreshold clusters were brain regions significantly connected to brain activations across experiments.

**Specificity of ANM**

To test whether the above obtained activation network maps were specific to facial emotion processing, we compared unthresholded activation network maps (experiment-level mean activation network z maps) of facial emotion processing with those of non-emotional cognitive processing using a voxelwise two-sample t-test implemented in Statistical non-Parametric Mapping (SnPM13, http://warwick.ac.uk/snpm). We corrected multiple comparisons using permutation-based testing with 5000 permutations and cluster-level FWE corrected P < 0.05 (cluster-forming threshold at voxel-level p < 0.001). To ensure that the results were robust to different statistical approaches, analyses were repeated using a Liebermeister test implemented in NiiStat software (www.nitrc.org/projects/niistat), which compared the above experiment-level binarized activation network t maps of each experiment with those of non-emotional cognitive processing. As recommended previously (Karnath, Sperber, & Rorden, 2018), only voxels that survived in more than 10% of our binarized activation network maps were included in the statistical analysis. A total of 5000 permutations and voxel-level FWE corrected P < 0.05 for multiple comparisons were used.

**Replication analysis**

**Split-half replication**
To test for the internal reliability of our ANM results, we randomly divided all facial emotion processing experiments into two equal subgroups. 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.

**Replication using a different seed size**

To ensure that our network localization was independent of seed size, we repeated the analysis using a larger sphere size of 8 mm.

**Replication using another normative connectome dataset**

To ensure that our results were independent of the normative connectome database used to derive activation network maps, we repeated our ANM procedure using 1000 normative connectomes of healthy subjects from another publicly available database—the Genome Superstruct Project (GSP) (Holmes et al., 2015; Yeo et al., 2011). The preprocessing steps of the GSP dataset are described in the Supplementary Methods.

**Distribution of facial emotion processing network in basic network modules**

To determine which network modules comprise the identified facial emotion processing network, we computed the percentage of regions in each of the well-known seven network modules identified by Yeo et al. (2011).

**Relevance to TMS stimulation 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 (i) involved healthy adult subjects; (ii) used a facial emotion processing task and reported disruption (either reduced accuracy or increased reaction time); (iii) delivered TMS to the scalp covering the cerebral cortex; (iv) 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 due to 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 region of interest (ROI)-based sensitivity and specificity analyses. Briefly, a modeled stimulation-site map was created by combining all spherical seeds of stimulation sites as described above. We also created a modeled control site map using vertex coordinates extracted from finally selected TMS studies since all these studies used vertices as control sites. As described above, for each of the 1000 normative subjects in our HCP dataset, we calculate Pearson's correlation coefficient between
the average time course of voxels within the modeled activation map and that within the modeled stimulation/control site map. Then, these r values were converted to a normal distribution using Fisher's r to z transform and averaged to obtain the experimental-level z score. Finally, group comparisons were analyzed 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 maps disrupting facial emotion processing were significantly more connected to activation maps of facial emotion processing than to activation maps of non-emotional cognitive processing. Second, we tested whether TMS stimulation maps disrupting facial emotion processing were significantly more connected to activation maps of facial emotion processing than to vertex control maps.

**Relevance to gray matter volume (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, Opmeer, van Tol, Goerlich, and Aleman (2018) 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 centered on each coordinate and combined these seeds to create a modeled atrophy map of alexithymia. Then, ROI-based sensitivity and specificity analyses were conducted to test whether the modeled atrophy map of alexithymia was functionally connected to activation maps 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 (Adolphs, Tranel, Damasio, & Damasio, 1994; Brierley, Medford, Shaw, & David, 2004; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004), ventromedial prefrontal cortex (vmPFC) (Adolphs, 2014; Roy, Shohamy, & Wager, 2012; Willis, Palermo, McGrillen, & Miller, 2014; Wolf, Philipp, Motzkin, Baskaya, & Koenigs, 2014), and insula (Boucher et al., 2015) disrupt a person's ability to recognize emotional facial expressions. Anatomical ROIs for these three brain regions were defined according to Automated Anatomical Labeling (AAL) template labels (Tzourio-Mazoyer et al., 2002). To test whether these brain regions are functionally connected to brain activations during facial emotion processing and whether these functional connectivities are specific compared with non-emotional cognitive processing, ROI-based sensitivity and specificity analyses were performed as above.

**Results**

A total of 141 studies with 230 experiments comprising 3138 participants were included in our study (Table 1).
Table 1
Descriptive statistics of the emotions included in the meta-analyses.

| Emotion | Studies | Experiments | Participants | Foci |
|---------|---------|-------------|--------------|------|
| Anger   | 37      | 39          | 1226         | 224  |
| Aversion| 2       | 2           | 88           | 16   |
| Disgust | 24      | 24          | 415          | 202  |
| Fear    | 75      | 78          | 1799         | 620  |
| Happiness| 43    | 44          | 1156         | 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   |

**ALE meta-analysis of brain activation**

The ALE meta-analysis was carried out on five basic emotions: anger, disgust, fear, happiness, and sadness. We did not perform the analysis on the other basic emotion—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 do engage more often than by chance (Fig. 2a). However, only 21% of experiments in anger (8/39), 29% of experiments in disgust (7/24), 37% of experiments in fear (29/78), 25% of experiments in happiness (11/44), and 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. Between emotions, no brain regions displayed consistent activation across all 5 basic emotions, and only the left amygdala showed activation in 4 of the 5 basic emotions. The spatial correlation matrix between each pair of unthresholded z maps obtained from the ALE meta-analysis illustrated few similarities in activation patterns among the basic emotions (mean r = 0.21, Figure S2).

**Network localization of individual basic emotions**

Next, we performed ANM to determine whether these highly inconsistent brain activations across experiments localized to a common network. The resulting activation network overlap maps showed that, within each basic emotion, over 92% of experiments in anger (36/39), 88% of experiments in disgust (21/24), 81% of experiments in fear (63/78), 66% of experiments in happiness (29/44), and 78% of experiments in sadness (18/23) were functionally connected to the same region (Fig. 2b; Table S2).
Among basic emotions, the spatial correlation of unthresholded overlap maps between each basic emotion illustrated that the similarities of network patterns were very high—ranging from 0.77 to 0.87 (mean r = 0.82); these similarities were significantly higher than those determined by the ALE meta-analysis (p < 0.0001, Figure S2).

Similar results were found in activation network t maps obtained using the second approach, with the temporal pole also being the most significantly connected region and with considerable similarities of network patterns among the basic emotions (mean r = 0.85, Fig. 2c and Table S3). 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 r = 0.82), indicating that the resulting network maps were highly consistent across these two complementary approaches.

**Network localization of emotion-general processing**

To identify the emotion-general brain network, experiments of all emotions were pooled and analyzed using the same approach as described above. Since the resulting activation network overlap map and t map are very similar, to make full use of the high statistical power afforded by the large sample size (n = 230) and to avoid arbitrariness when setting the overlap threshold in the alternative approach, we decided to make the activation network t map our primary result in the following analysis. 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 (FFA), 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. Specificity analysis showed that connectivity to these regions was mainly specific compared with brain activations during non-emotional cognitive processing (Fig. 3c). Similar connectivity patterns were found when different statistical approaches were used (Figure S3).

Subsequent examination of the spatial distribution of these facial emotion-related regions in the seven well-known functional network modules identified by Yeo et al. (2011) showed that facial emotion processing was specifically associated with the default mode network (DMN), limbic network (LN), and visual network (VN) (Fig. 3c).

The network pattern of facial emotion processing was highly reliable when split into two randomized subgroups (spatial correlation r = 0.98, Figure S4) or when a larger seed size of 8 mm (spatial correlation = 0.998, Figure S5b) was used. Also, the network pattern of facial emotion processing was independent of the normative connectome datasets used. The regions identified using the normative connectome of 1000 subjects from the HCP were still clearly present in networks derived using GSP datasets (Figure S5c). The connectivity patterns between these two datasets were also highly similar (spatial correlation = 0.88).

**Network localization of TMS stimulation sites that disrupt 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 (Table S1; Figure S6). 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 2 seeds were within 6 mm of the nearest cluster (Fig. 4a).

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 part of a common functionally connected brain network, which overlapped very well with our facial emotion networks derived from brain activations (Dice index = 0.57). ROI-based sensitivity and specificity analysis indicated that stimulation sites that disrupt facial emotion processing were significantly connected to activations of facial emotion processing, and this connectivity was specific when compared with activations of both non-emotional cognitive processing (p < 0.001) and vertex control sites (p < 0.001, Fig. 4c).

**Relevance to GMV reduction in alexithymia**

Four peak coordinates were reported in Xu's study (Xu et al., 2018). Three of the four spherical seeds centered on these coordinates overlapped with our localized facial emotion processing network, and the remaining seed was within 5 mm of the nearest cluster. Two spherical seeds overlapped with the emotion-specific network derived from specificity analysis. ROI-based sensitivity and specificity analysis showed that brain activations under facial emotion processing were significantly connected to brain regions associated with alexithymia (p = 0.002); this connectivity was specific to brain activations during facial emotion processing when compared with non-emotional cognitive processing (p < 0.001, Fig. 5).

**Relevance to lesions that disrupt facial emotion processing**

Both the insula and 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 analysis showed that all three regions were significantly connected to brain activations during facial emotion processing. For the amygdala and vmPFC, but not the insula, this connectivity was specific compared with non-emotional cognitive processing (Fig. 6).

**Discussion**

Using the novel ANM technique, we obtained several noteworthy results. First, though the results of discrete-brain-based ALE meta-analysis indicated that reproducibility was relatively low across neuroimaging findings, they were indeed highly reproducible in terms of connectivity and network. Second, the shared brain networks across five basic emotions supported conceptual act theory rather
than basic emotion theory. Third, our network localization of facial emotion processing aligned remarkably well with brain stimulation sites—and the network derived from it—that disrupt facial emotion processing in healthy individuals. Finally, brain structural abnormalities associated with alexithymia and brain lesions that disrupt facial emotion processing were functionally connected to regions activated during facial emotion processing.

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 (Darby et al., 2019; Fox, 2018; Tetreault et al., 2020; Weil et al., 2019). However, 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 noted among functional imaging studies, but not the only reason. We propose that factors that cause low reproducibility can be categorized into two groups. The first is the “false-positive” group. This group can lead to the activations of brain regions that are not associated with the target brain function. For example, the noise signal and incorrect implementation of experimental procedures. Factors of this group could reduce the reproducibility of both traditional activation localization studies and our network localization. This may explain why we did not find brain regions that were connected to all experiments. 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 sizes, only the strongly activated neural components (such as hub regions) of the network could survive the statistical threshold, leaving 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 demand on the same psychological unit, thus different 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 (1000 subjects) to recover the undetected brain components of the network, thus eliminating the effect of false-negative factors (but not false-positive factors) and boosting reproducibility across different studies.

Previous LNM studies mostly relied on t-value thresholds to define whether two regions were connected. After that, the thresholded t maps were binarized and overlapped before being thresholded again at a certain percentage. The strength of this approach is that 1) the binarized maps could be compared intuitively with traditional binarized lesion maps, and 2) the resulting network could be interpreted straightforwardly (connected or not) (Cohen & Fox, 2020). The drawback is that the localized network is largely dependent upon the selection of the t-value threshold and sample size of the normative connectome—both of which were inconsistent across previous LNM studies and lack clear guidelines (Sperber & Dadashi, 2020). Furthermore, when thresholding the overlap map of the binarized t map, the thresholds were arbitrary and inconsistent across previous LNM studies (ranging from 55–93%). To
overcome these limitations, we adopted an additional approach to conduct sensitivity analysis. We used a one-sample t-test to combine these experiment-level mean z maps, which were far less dependent upon the sample size of the normative connectome database. Then, we could resort to common practice in statistical parametric mapping when thresholding the group-level activation network t map, and the resulting suprathreshold clusters could be thought of as brain regions that were significantly connected to activated regions across experiments. The strengths and weaknesses of these two approaches are complementary. Using both approaches made our results more robust.

Our ANM analysis revealed a complex and interconnected network involved in facial emotion processing. This network includes well-known emotion-related regions such as the amygdala, insula, medial prefrontal cortex, and thalamus. 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 FFA. It is consistent with previous findings that visual cortical activity and emotion are intertwined (Kragel, Reddan, LaBar, & Wager, 2019). 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 connection with the limbic and paralimbic systems (Duvernoy, 1999; Mesulam, 2000). By binding highly processed perceptual information to visceral emotional responses, it takes part in both social and emotional processing, including facial recognition (Damasio, Tranel, & Damasio, 1990) and theory of mind ((Saxe & Powell, 2006), see Olson, Plotzker, and Ezzyat (2007) for a review). Specificity analysis revealed that facial emotion processing specifically activated the LN, VN, and DMN. These findings are consistent with previous studies: The LN is well known for its role in emotion processing; The VN, which includes the FFA, is presumably responsible for face-related visual information during facial emotion processing; the DMN plays a key role in constructing discrete emotion processing (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Satpute & Lindquist, 2019; Vytal & Hamann, 2010), and damage to DMN nodes impairs one's ability to identify facial expressions of discrete emotions (Campanella, Shallice, Ius, Fabbro, & Skrap, 2014; Dal Monte et al., 2013; Jastorff et al., 2016; Krause et al., 2009; Lindquist, Gendron, Barrett, & Dickerson, 2014; Tsuchida & Fellows, 2012).

A longstanding controversy in neuroimaging studies of emotion has centered on whether different emotions 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” (Hamann, 2012; Lindquist & Barrett, 2012; Lindquist et al., 2012). 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 meta-analysis indicated that different basic emotions share a common set of neural components. This finding provides 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. This finding is also in line with prior works that showed that common brain regions and networks are consistently activated across different basic emotions (Kober et al., 2008; Lindquist et al.,
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, insula being the most connected regions. All these results implied that exploring brain-behavior 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-behavior mappings at the level of individual brain regions is less productive since complex behaviors are always collectively supported by networks of brain regions (Pessoa, 2014, 2018).

Functional neuroimaging research has long been criticized for providing only correlational information 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 behavior 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 results of ANM are also consistent with the results of VBM studies of alexithymia and lesion-behavior 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. 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, TMS, VBM, and lesions—make us confident in the validity of ANM as a novel 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” (Alexander-Bloch, Raznahan, Bullmore, & Giedd, 2013; Honey, Thivierge, & Sporns, 2010; Kelly et al., 2012).

Limitations

There are several limitations to our study. First, as with previous coordinate-based network mapping studies, we created spheres centered 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 modeled activation map. A potential solution to this limitation would be to extract ROIs from activation-based or connectivity-based parcellation atlases (e.g., the Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA)) 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 experiments, and 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 temporally unstable, are more vulnerable to methodological heterogeneity, and are hampered by noises abundant in functional neuroimaging. All these features can introduce noise into our ANM results. However, these factors should bias us against finding the present common brain network. Finally, the present study was limited to only one psychological function. To extend the validity of this technique, it will be necessary to use it to localize networks of other psychological functions. Like facial emotion processing, many other psychological functions, such as vision (Kim, Kay, Shulman, & Corbetta, 2018; Sehatpour et al., 2008), memory (Sestieri, Corbetta, Romani, & Shulman, 2011; Vincent et al., 2006), language (Fedorenko & Thompson-Schill, 2014), attention (Ptak, 2012), and social cognition (Lee, Farrow, Spence, & Woodruff, 2004), 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.

Declarations

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

The computer code that supports the findings of this study is available from the corresponding author upon reasonable request.

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**Figures**
Figure 1

Activation network mapping technique. (a) Four-millimeter spheres centered on peak coordinates reported in each experiment were created and combined to obtain modeled activation maps. (b) Experiment-level functional connectivity t maps were computed using a large normative human connectome and then thresholded at voxel-level familywise error (FWE)-corrected P < 0.05. (c) The above functional connectivity t maps were binarized and overlapped and then thresholded at 60% to identify regions functionally connected to more than 60% of the experiments. (d) Experimental-level mean functional connectivity z maps were computed for each experiment using the same large normative human connectome. (e) The above functional connectivity z maps were combined using a one-sample t-test to obtain an activation network t map and then were thresholded to identify brain regions significantly connected to facial emotion processing experiments.
Network localization partly explains the poor reproducibility of functional neuroimaging studies of facial emotion processing. (a) ALE meta-analysis of each basic emotion. Though with a large sample size, the significantly activated regions were scarce for several emotions. Furthermore, all these significantly activated regions were driven by a small number of experiments (10-37%). (b) In contrast, ANM based on these same studies showed high reproducibility with a large proportion of experiments connected to the same set of brain regions. (c) Activation network t maps created using the alternative “one-sample t-test” approach are similar to activation network overlap maps. There were no significant clusters in sadness.
Figure 3

Network localization of emotion-general processing and its distribution in brain network modules. (a) Activation network overlap map shows regions functionally connected to more than 60% of the facial emotion processing experiments. (b) Activation network t map shows regions functionally connected to brain activations of facial emotion processing and its distribution in 7 basic functional network modules identified by Yeo et al. (2011). (c) Nonparametric voxelwise t-test mapping results showing regions in which brain activations of facial emotion processing were significantly more connected than connectivity of brain activations during non-emotional cognitive processing and its distribution in 7 basic functional network modules.
Figure 4

The network derived from brain activations during facial emotion processing aligns well with TMS stimulations disrupting facial emotion processing. (a) Seven representative spheres (of 13 in total) centered on stimulation sites that disrupted facial emotion processing. Eleven of 13 spheres overlapped with a network derived from brain activations during facial emotion processing (this network is the same as that in Figure 3a). (b) Network derived from these stimulation sites using the ANM technique. The network aligns very well with the network derived from brain activations. (c) Stimulation sites that disrupted facial emotion processing were significantly more connected to activations of facial emotion processing than with activations of non-emotional cognitive processing (left; p < 0.001). This connectivity was also specific to stimulation sites compared with vertex control sites (right; p < 0.001). Error bars represent standard error of the mean.
Figure 5

Relevance to structural abnormalities in alexithymia. Three of the 4 spheres centered on peak coordinates of structural abnormality in patients with alexithymia, a subclinical deficiency in the ability to identify and express emotions (green; only 2 representative spheres are shown), overlap with our localized network. Regions activated during facial emotion processing are functionally connected to brain regions in which gray matter volume is associated with alexithymia. These connectivities are specific to regions activated during facial emotion processing compared with regions activated during non-emotional cognitive processing. Error bars represent standard error of the mean.

Figure 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 analysis also showed that regions activated during facial emotion processing were functionally connected to the amygdala (a), ventral media prefrontal cortex (b), and insula (c). For the amygdala and vmPFC, these connectivities were specific to regions activated during facial emotion processing compared with regions activated during non-emotional cognitive processing. Error bars represent standard error of the mean.

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