REVIEW

Activation Likelihood Estimation Neuroimaging Meta-Analysis: a Powerful Tool for Emotion Research

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Abstract: Over the past two decades, functional magnetic resonance imaging (fMRI) has become the primary tool for exploring neural correlates of emotion. To enhance the reliability of results in understanding the complex nature of emotional experiences, researchers combine findings from multiple fMRI studies using coordinate-based meta-analysis (CBMA). As one of the most widely employed CBMA methods worldwide, activation likelihood estimation (ALE) is of great importance in affective neuroscience and neuropsychology. This comprehensive review provides an introductory guide for implementing the ALE method in emotion research, outlining the experimental steps involved. By presenting a case study about the emotion of disgust, with regard to both its core and social processing, we offer insightful commentary as to how ALE can enable researchers to produce consistent results and, consequently, fruitfully investigate the neural mechanisms underpinning emotions, facilitating further progress in this field.

Keywords: affective mapping, BrainMap, quantitative synthesis, coordinate-based meta-analysis, fMRI, affective neuroscience

Introduction

Understanding the functional dynamics of neuronal populations involved in emotional experiences is crucial for comprehending the complexity of emotions and their role in various mental phenomena, such as information processing, memory, and decision-making.[1] There are different methods capable of providing images of the activated areas of the brain by investigating the localization of neuronal structures involved in a given emotional phenomenon. The main human brain imaging techniques used for functional localization are functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), electroencephalography (EEG), single photon emission computed tomography (SPECT), and functional near-infrared spectroscopy (fNIRS).[2–7]

The past 20 years of neuroimaging research have yielded thousands of studies correlating brain regions with human emotions. A graphical overview can be found in Figure 1. These studies have revealed the involvement of several brain structures in different emotional processes, including the anterior cingulate, anterior insula, amygdala, medial prefrontal cortex, occipital temporal cortex, and the orbitofrontal cortex.[8–10] One major area of inquiry has examined whether emotions arise from a discrete set of basic emotions (eg, happiness, sadness, anger, and fear) or if they emerge through combinations of fundamental dimensions like salience and valence.[11–15] Furthermore, neuroscientists have dedicated their efforts to studying the intricate relationship between emotions and various brain disorders. By meticulously examining the neurofunctional variations associated with emotional aspects in clinical populations, neuroscientists actively pursue valuable insights into how emotional states impact the brain, overall well-being, and the progression of various illnesses.[16–18]
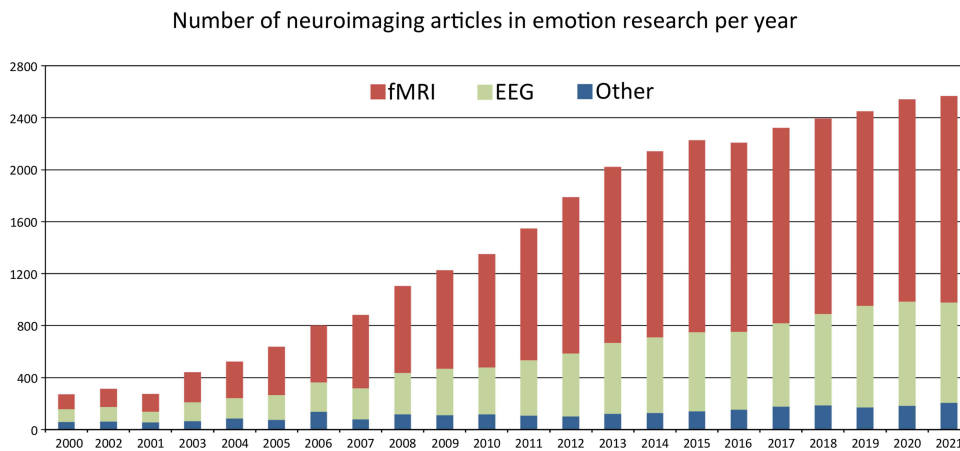
Number of neuroimaging articles in emotion research per year

Figure 1 Number of published articles per year in PubMed search engine (https://pubmed.ncbi.nlm.nih.gov/) for neuroimaging techniques in the field of emotion research. **Abbreviations**: fMRI, functional magnetic resonance imaging; EEG, electroencephalography; PET, Other positron emission tomography; SPECT, single-photon emission tomography; MEG, magnetoencephalography.

The field of affective neuroscience is currently witnessing a lively debate about the nature of emotions. On the one hand, some authors believe that emotions are constructed by means of interoceptive processes, cultural concepts, and the social context.[19] This view denies that there are brain circuits dedicated to specific emotions; it also rejects the idea that the so-called primary or basic emotions are genetically predetermined. On the other hand, other authors believe that emotions are embedded in behavioral patterns that are driven by "primary emotional systems".[20] According to this perspective, seven primary emotional systems (Search, Fear, Anger, Care/Food, Sadness/Pain, Sexuality, and Play), which are genetically programmed, activate specific and basic emotional schemes. For instance, The Search system activates the emotions of pleasure and surprise. The Fear system activates the emotions of fear. The Anger system activates the emotion of anger. The Care/Food system activates the emotions of disgust, contempt or pleasure. The Sadness/Pain system activates the emotions of pain or sadness. The Sexuality system activates the emotion of pleasure for sexual arousal and enjoyment. The Play system activates the emotion of pleasure for imagination and, if the game is shared, the pleasure that comes from participating in a social activity. Each primary emotional system is associated with specific neural correlates and networks, which have important underpinnings in subcortical structures such as the brain stem.[21] As there are different ways to define emotions (eg, positive vs negative, primary and secondary, etc.), probably the best way to account for their multifarious aspects is to integrate complementary perspectives and methods of investigation. This introductory guide constitutes a further methodological tool that fits into the integrated framework for investigating the human affectome recently proposed by a large group of scientists.[22]

In this work, the focus will be on fMRI, a technique that has provided a wealth of data, which has contributed to elucidating the brain areas activated by a given stimulus, during a task, or following an emotional experience. However, several aspects of fMRI (and neuroimaging methods in general) limit the validity as well as the generalization of individual studies. One well-known limitation is the frequently small number of subjects participating in experiments, with a mean sample size of 23 participants per study.[23] This limited sample size poses challenges in terms of statistical power and reproducibility of the fMRI findings.[24–26] Low statistical power refers to the decreased likelihood of detecting a true effect or relationship between variables when few data are available (as in the case of a small sample size). With a small number of participants, the ability to detect significant effects becomes diminished, potentially leading to false negatives or failing to identify genuine effects that may be present in the population of interest. Poor reproducibility, on the other hand, pertains to the consistency of obtaining the same or similar results when repeating an experiment using the same experimental procedures and conditions. If the results of an fMRI study cannot be reliably reproduced, it raises concerns about the robustness and generalizability of the findings.[25] Moreover, differences in experimental protocols[27] and fMRI data processing pipelines[28] additional sources of heterogeneity. Considering this intricate landscape, it becomes evident that relying solely on the activation of a brain area in a single neuroimaging experiment is insufficient to establish a reliable association between the observed phenomenon and its neural correlates.[26,29]

There is, therefore, the need to integrate results from different studies to ensure consistency of data. Meta-analyses provide a method to precisely achieve this goal, as they review relevant experiments in the literature and combine their data in a quantitative manner to obtain results that are more consistent than those of the original studies.[30] Thus, the use of meta-analysis, in principle, increases the statistical power and reproducibility of findings.[31,32]

In the fields of human brain mapping and affective neuroscience, coordinate-based meta-analysis (CBMA) plays a crucial role in integrating findings from neuroimaging experiments focused on emotional phenomena. By pooling together results from studies employing various tasks and cohorts worldwide but targeting the same research question, CBMA can provide a comprehensive understanding of specific emotional domains.[7,33] Specifically, CBMA methodology enables the identification of brain areas that exhibit consistent activation across a range of fMRI tasks employed in emotion research. Unlike standard meta-analyses in other research domains that estimate effect sizes,[30] CBMA focuses on spatial reliability among multiple results.[34] This is due to the fact that, in neuroimaging studies, it is rare to have comprehensive three-dimensional (3D) maps of brain findings. Instead, researchers typically present their results as 3D points in study tables. These points, known as activation peaks or foci, represent the specific 3D locations in the brain where the highest level of activity was observed. The coordinates of these peaks are reported using a system called stereotactic coordinates (x, y, z foci), which provide a reference for the precise location of the brain activity. The goal of CBMA is to construct a map that represents the likelihood or probability of brain activation at different locations. This map is created by combining the activation peaks from multiple studies and estimating the probability of activation in each brain region. In simpler terms, CBMA is a way to piece together information from different studies and create a map of brain activity. This helps researchers understand which regions of the brain are consistently associated with certain tasks or conditions, even when full 3D maps are not available. Detailed methodological accounts can be found in Manuello et al[31] and in the following paragraphs.

Different methods have been developed in the last twenty years to perform fMRI meta-analyses starting from stereotactic coordinates of activation peaks.[35] The most common are the activation likelihood estimation (ALE),[36–38] the kernel density analysis (KDA) and multilevel KDA (MKDA),[27] and the seed-based d mapping (SDM).[39,40] In this review, we consider the ALE method, and its implementation in the freely available software GingerALE,[36–38] developed and maintained by the Research Imaging Institute of the University of Texas – Health Science Center San Antonio (http://www.brainmap.org/). The ALE is particularly notable for providing a rigorous environment that automates the estimation of spatial-unbiased distribution maps across fMRI experiments, mitigating the laboratory and group-level inhomogeneity.[41] Simulation studies have demonstrated that ALE offers superior spatial accuracy in aligning results with canonical image-based neuroimaging results compared to other CBMA methods.[42] Moreover, the ALE algorithm has undergone continuous enhancements over the past two decades.[36,43–47] These updates have contributed to its reliability and precision, cementing its role as an integral component of the Brainmap multi-platform resource,[48] which provides a set of neuroimaging software packages and supports a wide array of neuroinformatic operations.

In this context, our main goal is to present a clear and comprehensive overview of the CBMA approach and its application in the field of emotion research. In the following paragraph, we specifically focus on fMRI as the imaging technique of interest. Additionally, we aim to explain the underlying principles of CBMA, with a particular emphasis on the ALE method. In the last paragraph, we discuss the significance of CBMA in advancing our understanding of brain activations related to emotions. Here, we illustrate the main methodological steps involved in CBMA and, more broadly, demonstrate how the ALE technique can be utilized in emotion research. To provide a concrete example, we present a recently published case study that demonstrates the application of the ALE environment in the field of emotion research. By doing so, we aim to highlight the practicality and relevance of CBMA in enhancing our knowledge about the neural correlates of emotions.

Functional Magnetic Resonance Imaging Background

This section gives a very brief introduction to the steps involved in an fMRI experimental study, with a focus on emotion research. For a more detailed methodological account, please see Lindquist[49] and Poldrack, Mumford, and Nichols.[50]

At the basis of fMRI there is the fact that, because neurons have no cellular reserves of energy in the form of sugar or oxygen, energy needs to be provided to the brain areas characterized by high activity levels. The supply is operated

through the circulation of fresh blood towards those brain regions, technically called hemodynamic response. Once the oxygenated blood reaches its target the oxygen is promptly used by neurons. The shift from well-oxygenated to deoxygenated blood causes a reconfiguration of red blood cells which can be detected by magnetic resonance machines (due to the presence of iron in the blood). In fact, the signal captured and processed in MRI analyses is called blood oxygenation level-dependent (BOLD), telling therefore how brain regions are consuming oxygen from blood due to neuronal activity.[51] The general idea in fMRI is therefore to engage participants in a task (ie, task-fMRI) that is designed to demand a cognitive ability to be solved. The brain regions that were seen to require more blood supply during the task execution are therefore supposed to support the cognitive ability under investigation. When this approach is applied in the field of affective neuroscience, participants are typically asked to perform a series of emotional tasks or are exposed to emotionally evocative stimuli, such as images, videos, or sounds, while the scanner measures the BOLD signal. The signal is acquired over time, so to obtain a temporal profile. In order to allow a fine-grain resolution of the activity profile, the brain is divided into millimeters wide voxels (ie, a 3D version of the pixels) and BOLD is measured for each of them. Therefore, at the end of the experimental session it is known, for each participant, how each single voxel of its brain reacted over time while the emotional stimuli were shown.

While an in-depth description of the necessary procedures to move from raw data to final results is out of scope here, a few concepts need to be mentioned. First, when more than one participant was tested, their data have to be mapped to a common space. This is known as spatial normalization, and allows to make the participants' brains to be geometrically similar to a standard one (typically the Talairach atlas[52] or the Montreal Neurological Institute (MNI) atlas).[53] After this spatial normalization, one can assume that a given voxel represents (roughly) the same small portion of the brain across all subjects. At a second relevant step, it is necessary to distinguish between activity truly associated with the emotional task (or other stimulus of interest) and background noise, that is made of random activations unrelated with the fact that a stimulus was delivered to the subject. This is technically achieved by fitting a mathematical model (ie, a T-statistics) to the data of each voxel. The obtained numerical value tells us to what extent the activity of this given voxel is unlikely to be merely random or due to background noise, or in other words statistically significant. Due to biological constraints, these significant voxels usually appear grouped together to form clusters, rather than sparse across the brain. The peak of activity within each cluster, also known as a focus, is identified by determining the voxel with the highest level of activation. The location of each focus is reported using a system of x, y, z stereotactic coordinates.

Activation Likelihood Estimation

ALE is the CBMA method most employed worldwide,[54] as evidenced by over 1300 published articles in peer-reviewed journals (for the full list see also http://brainmap.org/pubs/). Its popularity is supported by the availability of GingerALE, a free and widely used software package implementation of the ALE algorithm.[48,55–57] For a more comprehensive guide, please refer to the user manual available at https://brainmap.org/ale/manual.pdf.

The fundamental premise behind ALE is to account for the uncertainty associated with determining the precise location of brain activations. In any fMRI experimental measurement, there exists a certain degree of imprecision. ALE tackles this issue by computing a probability for each voxel in the brain, representing the likelihood that it contains the specific brain activation being investigated. This probability is modeled as a series of Gaussian distributions, each one centered around a focus (ie, the estimated coordinates of the peak of activation measured in a given fMRI experiment). Consequently, the probability decreases as the distance from the center of the distribution increases.[38] In other words, when an experiment reports a focus at coordinates x,y,z the Gaussian distribution is built to assign a value of 1 to that voxel. Then, to account for spatial uncertainty, the voxels close to the peak receive a value of slightly less than 1, until reaching a probability of 0 when voxels are far enough from the peak to unlikely represent the real location of the maximum activation. This is repeated for each focus reported in one of the selected fMRI experiments, generating a so-called modeled activation (MA) map for each of them.[56] To obtain the final ALE map, the MA maps from all experiments are combined. The resulting ALE map provides information about the probability of finding brain activation in each voxel, offering insights into the areas of the brain more likely to be associated with the phenomenon under investigation. For a more detailed statistical description, see Supplementary Materials.

At the time ALE was developed, the final maps were used as is without further thresholding. However, it should be considered that this technique tests all the voxels in the brain simultaneously, giving rise to an issue of multiple comparisons. To mitigate this, therefore avoiding to increase the likelihood of false-positive findings,[45] several thresholding methods have been devised. The current standard is to adopt family-wise error (FWE) correction. Conceptually, this allows to test the values obtained in the ALE maps against what would be observed if foci were randomly distributed across the brain, rather than reflecting the peaks of activation obtained across the various experiments analyzed.[29] A further level of control can be added by imposing that the clusters in the final ALE map must be wider than the widest cluster obtained from, again, a random distribution of the foci across the brain[39] (for a more advanced description of thresholding procedures see Costa et al).[44] These correction methods enhance the reliability of results by reducing the risk of false-positive findings and improving the validity of identified consistent brain activation patterns.

Application of the Method in Emotion Research

ALE was originally introduced more than two decades ago[38] and has since become a valuable method in affective neuroscience for quantitatively analyzing neuroimaging data and uncovering consistent patterns of brain activity associated with emotional processes. Over the years, several influential studies have employed ALE to investigate various aspects of emotion processing.

To the best of our knowledge, the first ALE study in the field of affective neuroscience was conducted by Fusar-Poli et al,[58] who investigated the most consistent neural correlates of emotional facial processing. Their findings unveiled consistent activations in several brain regions, including visual, limbic, temporoparietal, and prefrontal areas, as well as the putamen and the cerebellum. These results highlighted the involvement of a network of regions spanning both sensory and higher-order cognitive processing in the perception and interpretation of emotional facial expressions. In a different line of research, Vytal & Hamann[59] conducted an extensive ALE meta-analysis to investigate the neural representation of basic emotions. The authors aimed to determine whether emotions such as fear, anger, disgust, sadness, and happiness are associated with consistent and distinguishable brain activations. The ALE method revealed compelling results. Each emotion demonstrated consistent neural correlates across studies, indicating reliable associations with specific brain regions. Furthermore, the activation patterns associated with each emotion were distinct, allowing for discrimination between them. These findings support the existence of consistent and discernible neural correlates linked to discrete basic emotions. Additionally, Li et al[54] conducted an ALE meta-analysis to investigate brain activation during facial emotion processing in patients with schizophrenia compared to healthy controls. The study aimed to address inconsistencies in previous findings regarding regional brain activation abnormalities in schizophrenia patients during emotion perception. The results indicated that both patients with schizophrenia and controls activated the bilateral amygdala and right fusiform gyri during facial emotion processing. However, the extent of activation in these regions was generally more limited in the schizophrenia samples. When directly compared to controls, patients with schizophrenia exhibited significantly less activation in the bilateral amygdala, parahippocampal gyrus, fusiform gyrus, right superior frontal gyrus, and lentiform nucleus. Notably, patients with schizophrenia showed under recruitment of the amygdala regardless of task design (explicit or implicit emotion elicitation), while differences in fusiform activation were observed primarily in explicit tasks. The findings suggest that a marked under recruitment of the amygdala, accompanied by limited activation throughout a social brain network (ie, ventral temporal-basal ganglia-prefrontal cortex), may contribute to the difficulties experienced by patients with schizophrenia in processing facial emotion. ALE was also used to investigate neural correlates of the processing of subliminal arousing stimuli through different modalities of presentation.[60] The results, showing the involvement of a distributed pattern encompassing the amygdala and the hippocampus, together with the salience network, elucidate the relationship between arousal and emotion.

These influential ALE studies collectively contribute to our understanding of the neural underpinnings of emotional processes. However, it is important to note that the studies mentioned here represent only a fraction of the extensive literature in this field. For a comprehensive list of emotion-related ALE studies, we recommend referring to the full compilation available at http://brainmap.org/pubs/. This resource provides a broader scope of research findings and further insights into the neural mechanisms underlying emotions.

Case Study: Do Consistent Brain Activations Occur in Disgust Processing?

In this section, we present an ALE coordinate-based meta-analysis as a proof of concept. Specifically, we selected the recent work of Gan et al[61] as a case study, who conducted an ALE meta-analysis on healthy human participants in order to i) identify spatially consistent patterns of neuronal activation engaged in general disgust processing, and ii) determine common and divergent patterns involved in core and social disgust processing. It is important to note that our intention here is not to replicate or extend their analysis but rather to showcase the main methodological design of the ALE environment in emotion research.

Disgust is considered a basic human emotion and a complex and evolutionary system of disease-avoidance mechanisms.[62] It is thought to have evolved to protect individuals from potentially contaminated substances and infections[63] through avoidant defensive behaviors (ie, core disgust).[64] On the other hand, with the advent of human society, the disgust response has also been crucial for the survival of conspecifics and successful socio-communicative relations (ie, social disgust).[64] Starting from the pioneering work of Phillips et al,[65] a wide amount of fMRI studies have investigated the neurofunctional substrate involved in disgust processing. Nonetheless, the precise localization of brain areas associated with this type of emotion remains a subject of debate. Additionally, the potential convergence and differences between core and social disgust processing remain largely unappreciated. These unresolved issues may be partially ascribed to the inherent limitations of single fMRI experiments, namely their methodological (eg, sample size, MRI field strength, acquisition protocol, task design, processing pipeline, etc.) and socio-demographic (eg, developmental stage of participants, cultural background, disgust propensity, etc.) factors.

Is there a convergent functional pattern that underlies disgust processing in the human brain? If so, which cortical, subcortical, and cerebellar regions are consistently recruited during core and/or social disgust processing? Gan et al[61] addressed these questions by conducting an ALE coordinate-based meta-analysis of published fMRI articles on this topic. Figure 2 provides a graphical overview of the primary methodological steps generally applicable to the ALE method, as well as those employed by the authors themselves.

Step 1: Literature Search

Using multiple combinations of appropriate keywords, the authors queried scientific databases (ie, MEDLINE, Web of Science) in search of eligible studies in peer-reviewed journals. This is the first critical point designed to ensure high sensitivity with respect to the research question. However, achieving precise yet extensive retrieval in biomedical and psychological systematic searches poses challenges due to the vast size of these databases, which now encompass approximately 33.8 million records.[66] Moreover, additional databases including PsycINFO, EMBASE, and Google Scholar may also be consulted, potentially increasing the total number of records to scrutinize. In this scenario, the application of search filters, Medical Subject Headings (MeSH) keywords, and advanced search strategies has proven effective in increasing the relevance and reducing the volume of records retrieved, without compromising the inclusion of potentially eligible articles.[67] It is important to note, however, that these strategies lack standardized rules due to the diverse research questions covered by CBMAs and depend heavily on expert-driven, meticulous searches of well-annotated literature. Therefore, it is considered good practice for different authors of the meta-analysis to conduct independent searches and subsequently evaluate the consistency of the results.[31]

The authors also queried the BrainMap database via Sleuth (https://www.brainmap.org/sleuth/),[48,55,56] a user-friendly software application capable of building standardized search algorithms and extracting in an automated manner meta-data of interest, including foci of the fMRI experiments in the stereotactic space adopted for the ALE analysis (details given in step 2). Although BrainMap contains approximately 20% of the current peer-reviewed neuroimaging literature,[68] we believe that its use in conjunction with the aforementioned databases generally represents a valuable choice for researchers. One of its key advantages is that it eliminates the need for researchers to individually inspect and analyze each selected fMRI study, which can be a time-consuming and error-prone process. By using BrainMap, researchers can avoid potential human errors in reporting foci, sample sizes, and the nature of the analysis conducted in each fMRI study. In essence, it provides a standardized and efficient approach to accessing and utilizing a wide range of fMRI data. For comprehensive guidelines on ensuring the traceability and replicability of meta-data in the field of CBMA, consult Manuello et al[31] and Müller et al.[32] These resources provide valuable insights into best practices for researchers in this field.
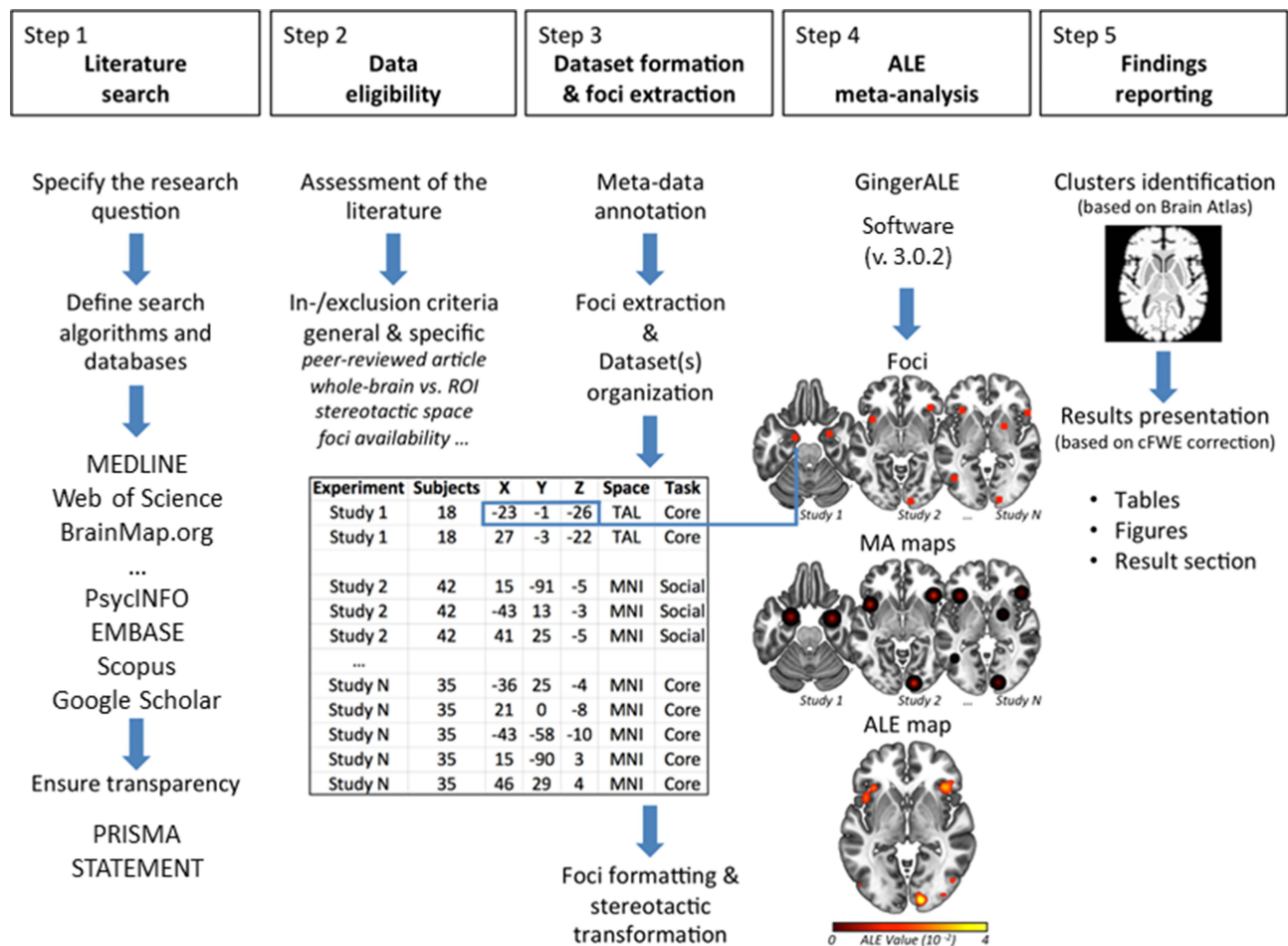
Figure 2 Workflow stages of the activation likelihood estimation (ALE) method.
Abbreviations: TAL, Talairach/Tourneaux space; MNI, Montreal Neurological Institute space; MA map, modeled activation map; ALE map, activation likelihood estimation map; cFWE, cluster-level family-wise error correction.

Finally, the authors manually checked the reference lists of the included studies to identify other eligible articles that could have been missed during the database searches. This constitutes another good practice because the meta-analytic approach should take into account, at least in theory, the entire current literature that is pertinent to the research hypothesis under consideration.

Step 2: Data Eligibility

After the identification of all potential data, the assessment of the identified literature starts. This procedure is essential for the systematic selection of experiments to be included in the final CBMA dataset. It also ensures the exclusion of neuroimaging data that fails to meet the a priori inclusion/exclusion criteria established by the authors. At this stage, it is considered best practice for two authors to independently evaluate the entire corpus of identified literature.[69] Additionally, it is typical for any disagreements between authors to be resolved through consensus, under the guidance of a third author.[70]

Usually, the first action consists of excluding, after a title- or abstract-level evaluation, non-original studies (ie review, systematic review, meta-analysis, letter to the editor, case report, etc.) and animal model studies. Of note, many authors discard articles published in non-English language journals to ensure easier replicability of the dataset worldwide.[54] Next, the full texts of the remaining articles should be downloaded for an in-depth evaluation. What inclusion or exclusion criteria should be taken into account? Inevitably, specific criteria depend on the particular research question and literature background. Beyond the affective domain or type of emotional task to select, specific criteria can relate to

the imaging methodology (eg, fMRI studies only or PET, SPECT, and fMRI studies) or to the characteristics of the experimental group (eg, healthy or clinical subjects; only a specific age rage/sex of subjects). For example, Gan et al[61] focused their analysis specifically on fMRI-based experiments involving healthy participants to study disgust processing. Their analysis exclusively incorporated data from visual stimuli to meticulously control for sensory modality, thus enabling effective comparisons between core disgust and social disgust. Moreover, in the case of multiple fMRI experiments from the same group of subjects within the study, the authors considered eligible only the most representative in the process of interest. This decision was motivated by an important methodological consideration. The ALE algorithm treats each fMRI experiment as an independent record,[71] meaning that data from the same participants may introduce a potential dependence that could compromise the validity of the final ALE results.[32]

In addition to specific criteria related to aspects of the topic, the design of the ALE method (and of CBMA in general) imposes that eligible experiments adhere to two specific requirements:

1. The findings reported in each fMRI experiment must be derived from imaging analyses that have covered the entire brain (ie, whole-brain analysis), rather than from small volume correction (SVC) or region-of-interest (ROI) analyses. ALE tests spatial convergence across experiments against a null hypothesis of random spatial associations across the whole brain, thus assuming that each brain voxel has the same chance of being activated.[36,45] Therefore, the inclusion of SVC and ROI findings violates this assumption and could lead to biased results for specific brain regions.[31,32]
2. The findings reported in each fMRI experiment must be in a stereotactic brain space (ie, Talairach or MNI) and accompanied by the peaks (foci) of significant effect observed. Although neuroimaging findings are usually normalized in a standard common space in order to evaluate the effects across the subjects' group, it is important to note that coordinates in MNI space differ from those in Talairach.[72] Thus, to reduce the spatial disparity between neuroimaging findings reported as MNI or Talairach coordinates, it is useful and recommended to convert data reported in MNI to Talairach space, or vice versa. This can be easily achieved through the transformation algorithm available in the GingerALE interface.[73] Moreover, assuming that whole-brain coverage and stereotactic space in an experiment have been verified, findings are still useless in the absence of the list of foci. Foci are frequently listed in a table in the Results section; alternatively, they can be obtained from the in particular when the corresponding analysis was not the principal aim of the study. When just a few foci are reported, the authors usually incorporate them into the main text.

Step 3: Dataset(s) Formation and Foci Extraction

Once the studies (and their fMRI experiments included) have been selected, the meta-data of interest should be extracted and organized into a.txt file format. Essential information, such as significant foci of activation and the number of subjects per fMRI experiment, is mandatory for conducting an ALE meta-analysis. It is crucial that the.txt file strictly adheres to the following input layout specifications to prevent the GingerALE application from treating the included experiments as missing data:

1. Begin each line containing meta-data must begin with "//".
2. The final line of meta-data for each included experiment must specify the number of subjects, using the format "Subjects=xx".
3. List x, y, z coordinates for each focus on separate lines, using a space to separate values and a period as the decimal separator, if necessary.
4. Include an empty line between the last focus of one experiment and the meta-data of the next.

For practical support to the ALE dataset formation see also https://github.com/Jordi-Manuello/CBMAT.[74]

It is also worth noting that the collection of other methodological and socio-demographic variables may be of interest as well. Type of emotional imaging/task/stimulus/contrast modality, presence/absence of multiple comparison correction of findings, analytic software employed, magnetic field strength, spatial smoothing of the data, male-female ratio,

intelligence quotient, and developmental stage of the participants are other optional meta-data that may be useful to perform sub-analyses of interest.

Again, the organization and reporting of the dataset should be transparent and detailed. The reader should be able to easily trace the original studies included and understand "how" the database is composed and/or sub-grouped. This may be achieved through the authors' presentation of tables in the manuscript or Supplementary Materials.

Step 4: Activation Likelihood Estimation Meta-Analysis

At this stage, the GingerALE application can be used to perform statistical analyses.[48,55,56] To assess the correct interpretation of the data, GingerALE requires only the foci.txt file (details on its format can be seen at http://www. brainmap.org/ale/manual.pdf). When the file has been uploaded, the number of stereotactic coordinates and the number of studies detected in the input are shown.

Regardless of the specific algorithm used for thresholding, GingerALE employs statistical analysis on the regions that surpass the chosen threshold. As mentioned earlier, just like individual neuroimaging studies, the ALE method requires correction for multiple comparisons. Uncorrected thresholding may offer higher sensitivity but also increases the risk of false positives. In neuroimaging CBMA, various methods are available for correcting multiple comparisons, but it is recommended to strike a balance between sensitivity and susceptibility to false positives.[32] In line with recent recommendations from the BrainMap team,[45,46] ALE results generally undergo family-wise error correction (FWE-c) for multiple comparisons. This correction involves a cluster-level inference with a significance threshold of $p < 0.05$ and a cluster-forming threshold of $p < 0.001$ at the voxel-level. By adhering to these guidelines, researchers can ensure more reliable and robust findings in their ALE analyses.

In their study, Gan et al[61] capitalized on a substantial body of literature to conduct a comprehensive ALE analysis on general disgust processing. This analysis included 71 fMRI experiments, comprising a total of 717 foci of activation and involving 1409 participants. The main ALE meta-analysis, which encompassed all the fMRI peer-reviewed experiments on disgust processing, revealed twelve consistent neuronal clusters of activation. These clusters were located in various brain regions, including the bilateral insula, amygdala, fusiform gyrus, middle occipital gyrus, right inferior occipital gyrus, right lingual gyrus, left inferior temporal gyrus, right inferior frontal gyrus, and left superior frontal gyrus. To visually illustrate these significant findings, refer to the upper panel of Figure 3. Interestingly, the authors discussed their findings in light of the multifaceted nature of the disgust response. The areas identified in the study may collectively support various simultaneous processes that contribute to a coordinated disgust reaction. These processes encompass different stages, including the initial detection of biologically salient stimuli in occipital visual regions, the early detection of threats, and the execution of defensive motor responses involving the amygdala and fusiform regions. Additionally, the identified regions are implicated in salience allocation and interoceptive awareness of the emotional state in the insula cortex, as well as the subjective experience and interpretation of the emotional state in prefrontal regions.

In contrast, the lower panel of Figure 3 illustrates the specific findings related to core disgust processing and social disgust processing sub-analyses. The authors identified ten clusters demonstrating robust activation for the core disgust sub-dataset, based on a subset of 41 experiments involving 402 foci and 897 participants. These clusters primarily encompassed the bilateral amygdala (with extension into the right globus pallidus) and inferior frontal gyrus, as well as the left fusiform gyrus, left inferior parietal lobule, and left inferior occipital gyrus extending into the adjacent lingual gyrus. As elegantly noted by the authors, this pattern of brain areas may reflect the activation of evolutionary defensive-avoidance circuits when individuals are directly exposed to potentially infectious and harmful stimuli. In fact, it is well-known that these areas are involved in the early detection of salient threats and initiate the physiological and behavioral defensive responses, facilitating rapid withdrawal from potentially dangerous situations.

Regarding social disgust processing involving a subset of 30 experiments, 315 foci, and 512 participants, the analysis revealed six significant clusters of robust activation. These clusters were located in the right insula and adjacent inferior frontal gyrus, bilateral fusiform gyrus, left superior temporal gyrus, and right middle occipital gyrus. Most of these identified regions have previously been linked to emotional face processing, encompassing both early face-processing stages and higher-level face perception processing. Additionally, other areas, such as the superior temporal regions, have
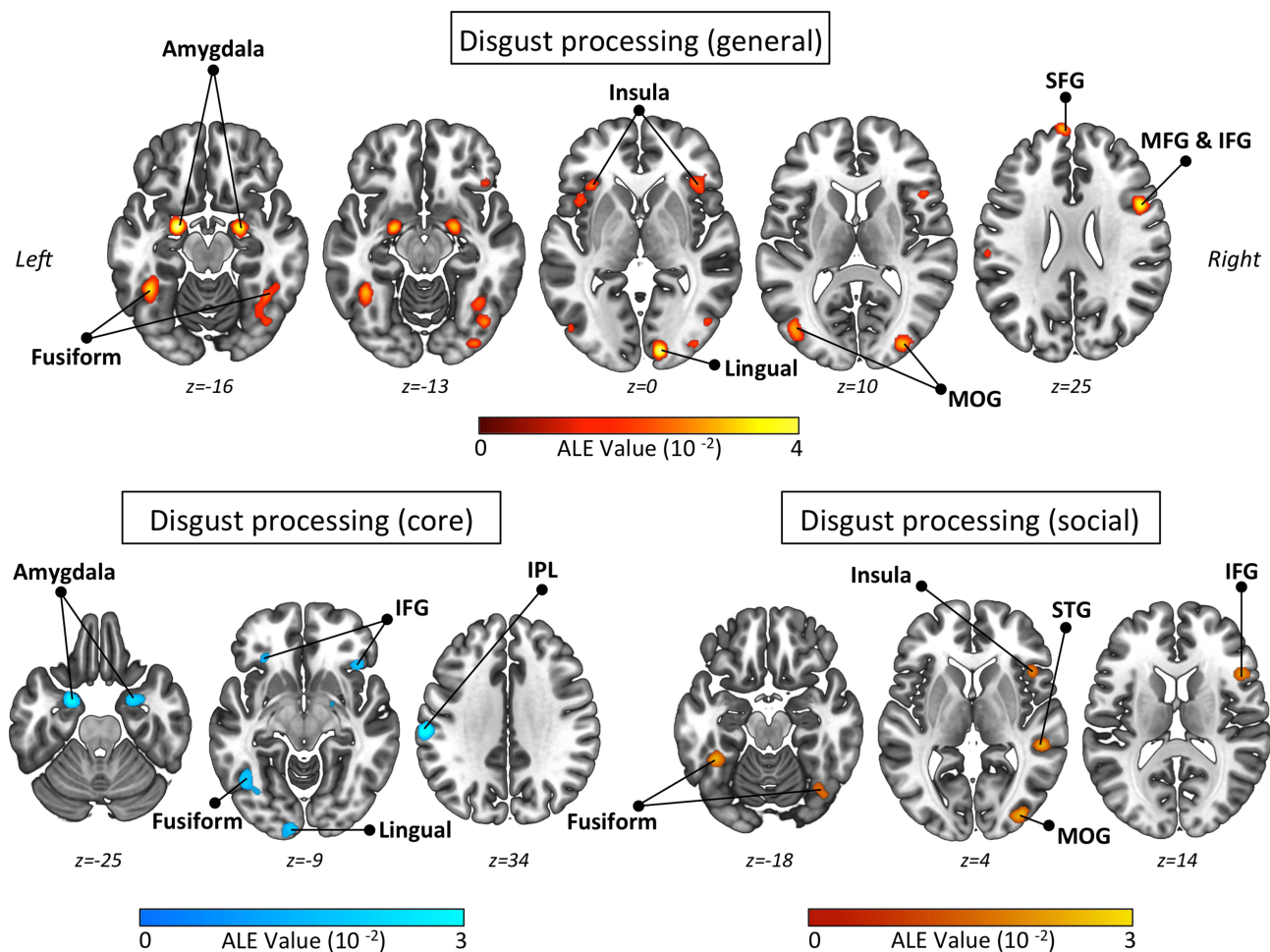
Figure 3 Brain clusters of spatially convergent patterns of activation in the general disgust processing dataset (main ALE analysis of Gan et al (2022);[61] top panel), core disgust processing dataset (subanalysis 1 of Gan et al (2022); bottom left panel), and social disgust processing dataset (subanalysis 2 of Gan et al (2022); bottom right panel). Results were FWE-corrected at 0.05 with cluster-forming value at p <.001 by Gan et al (2022) via GingerALE (v. 3.0.2.; http://www.brainmap.org/ale/). The activation likelihood activation (ALE) maps are visualized as axial slices (2-D cortical and subcortical view). Brain templates are in neurological convention (ie, R is right, L is left).
Abbreviations: ALE, activation likelihood estimation map; FEW, family-wise error correction; Fusiform, fusiform gyrus; Lingual, lingual gyrus; MOG, middle occipital gyrus; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; STG, superior temporal gyrus; z, number of the axial slice.

been prominently associated with social cognitive processes, including theory of mind and mentalizing. Interestingly, the authors' report highlights a distinct finding regarding social disgust processing. In contrast to several previous original fMRI studies, their ALE meta-analysis focusing on the social aspect did not demonstrate robust engagement of the amygdala. This deviation from prior findings adds to the evolving understanding of the neural mechanisms underlying social disgust processing.

An additional feature of GingerALE is its capability to conduct contrast analysis, enabling statistical comparisons between different datasets to identify common and divergent ALE patterns. To illustrate this feature, we can consider the contrast analysis performed by Gan et al.[61] In their study, the authors compared and contrasted the previously generated ALE findings of core disgust processing and social disgust processing. This analysis allowed for a systematic examination of the overlapping and distinct brain activation patterns associated with these two facets of disgust processing. The authors revealed robust activation of the right inferior frontal gyrus (extending into the anterior insula) during both core and social disgust processing. They also observed stronger recruitment of left hemisphere regions (ie, the left inferior frontal gyrus, globus pallidus, fusiform gyrus, and lingual gyrus) specifically in core disgust compared to social disgust. Conversely, a right hemispheric predominance was found for social disgust compared to core disgust, involving the right inferior frontal gyrus, precentral gyrus, superior temporal gyrus, and middle occipital gyrus. A graphical overview can be found in Figure 4. Interestingly, while the authors did not have specific a priori hypotheses about lateralization, their
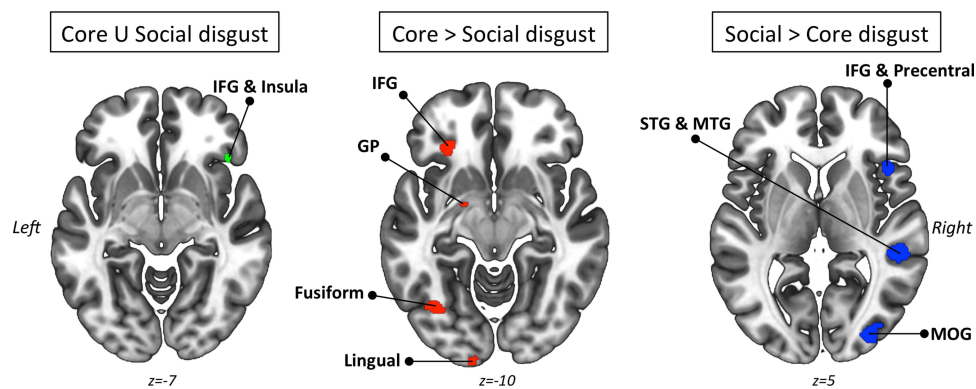
Figure 4 Conjunction and contrast analyses between core and social disgust processing datasets as performed by Gan et al.[61] Left panel: Convergence of activation between core and social disgust processing datasets (green color represents ALE values). Central panel: Compared to the social disgust dataset, activations are exclusively present in the core disgust dataset (red color represents ALE values). Right panel: Compared to the core disgust dataset, activations are exclusively present in the social disgust dataset (blue color represents ALE values).

Abbreviations: ALE, activation likelihood estimation map; IFG, inferior frontal gyrus; Precentral, precentral gyrus; GP, globus pallidus; Fusiform, fusiform gyrus; Lingual, lingual gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; MOG, middle occipital gyrus; z, number of the axial slice.

findings align with previous research indicating a left lateralization of withdrawal-related activity and a right lateralized network involved in conscious emotional perception. However, the discovery of a left-lateralized withdrawal network in this study is a novel finding that challenges prevailing neuronal models of approach/avoidance.

Step 5: Reporting of the Findings

In the final step of the analysis, the ALE computation outputs are generated by the GingerALE software package. The anatomical labels of the Talairach Daemon (http://www.talairach.org)[75] are assigned to the peaks of each cluster in the results map. It is important to clarify that in the ALE analysis, the labeling process for assigning anatomical labels to the peaks of each cluster is automated and data-driven rather than manually performed by the researchers. Additionally, a table is generated, providing various details about the identified clusters, such as their x, y, z coordinates, the number of significant voxels, the corresponding brain area names, and x, y, z statistical information regarding cluster formation. For a more comprehensive description, please refer to the user manual available at https://brainmap.org/ale/manual.pdf.

The GingerALE software saves the output maps in the NIfTI format (http://nifti.nimh.nih.gov), which can be easily read by various functional neuroimaging software packages. Additionally, the resultant ALE maps can be disseminated to the broader research community by uploading them to online neuroimaging repositories, such as the Archive of Neuroimaging Meta-analyses (ANIMA).[76] This dissemination is advantageous as it allows these maps to serve as reliable prior data for designing subsequent task-based fMRI studies. Furthermore, they can be employed as ROI in studies exploring functional connectivity or in various seed-based analyses,[77] including connectomics.[78,79] This enhances the utility of ALE maps in advancing neuroimaging research by facilitating shared resources and collaborative scientific inquiry.

Concluding Remarks

In conclusion, the ALE method has emerged as a crucial tool in emotion research and affective neuroscience, providing a powerful and quantitative approach to investigating the neural correlates of emotions. By integrating data from multiple neuroimaging studies, ALE provides a comprehensive understanding of the consistent patterns of brain activity associated with emotional processes under investigation. This method has allowed researchers to overcome the limitations of individual fMRI studies, such as small sample sizes and heterogeneity in experimental protocols, thereby enhancing the reliability and generalizability of findings. ALE has been instrumental in uncovering reliable neural activations related to emotional facial processing, basic emotions, and differences in emotion processing across healthy and clinical populations, just to name a few. It has significantly contributed to our understanding of the neural underpinnings of emotions, highlighting the specific brain regions involved and shedding light on the complex interplay

between emotions and cognition. Moving forward, the continued application and advancement of the ALE method[43,44] in emotion research promise to further deepen our understanding of the intricate mechanisms underlying human emotions.

Author Contributions

TC: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review and editing. MF: Conceptualization, Methodology, Supervision, Writing – original draft. JM: Methodology, Writing – review and editing. AC: Writing – review and editing. AN: Writing – review and editing. LM: Writing – review and editing. FC: Supervision, Writing – review and editing. PTF: Supervision, Writing – review and editing. DL: Conceptualization, Investigation, Supervision, Methodology, Visualization, Writing – original draft, Writing – review and editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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