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Multiple large-scale neural networks underlying emotion regulation

Carmen Morawetz[a,*], Michael C. Riedel[b], Taylor Salo[c], Stella Berboth[d], Simon B. Eickhoff[e,f], Angela R. Laird[b], Nils Kohn[g]

[a] MR Center of Excellence, Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria
[b] Department of Physics, Florida International University, Miami, FL, USA
[c] Department of Psychology, Florida International University, Miami, FL, USA
[d] Department of Education and Psychology, Freie Universität Berlin, Germany
[e] Institute of Systems Neuroscience, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[f] Institute of Neuroscience and Medicine, Brain & Behaviour (INM-7), Research Centre Jülich, Jülich, Germany
[g] Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmengen, the Netherlands

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ABSTRACT

Recent models suggest emotion generation, perception, and regulation rely on multiple, interacting large-scale brain networks. Despite the wealth of research in this field, the exact functional nature and different topological features of these neural networks remain elusive. Here, we addressed both using a well-established data-driven meta-analytic grouping approach. We applied k-means clustering to a large set of previously published experiments investigating emotion regulation (independent of strategy, goal and stimulus type) to segregate the results of these experiments into large-scale networks. To elucidate the functional nature of these distinct networks, we used functional decoding of metadata terms (i.e. task-level descriptions and behavioral domains). We identified four large-scale brain networks. The first two were related to regulation and functionally characterized by a stronger focus on response inhibition or executive control versus appraisal or language processing. In contrast, the second two networks were primarily related to emotion generation, appraisal, and physiological processes. We discuss how our findings corroborate and inform contemporary models of emotion regulation and thereby significantly add to the literature.

1. Introduction

Experiencing emotions is part of our daily life. Sometimes, these emotions can be intense, and we need to control them. Emotion regulation (ER) describes our ability to effectively manage emotional experiences, regardless of whether we need to down-regulate negative emotions or would like to up-regulate positive ones. Effective ER has been associated with a number of positive outcomes such as an increase in general well-being, performance at work and personal and professional relations, and most importantly, it supports our mental and physical health (Eftekhari et al., 2009; Gross and John, 2003; Gross and Muñoz, 1995). In contrast, deficits in ER are observed in severe psychological disorders such as depression and anxiety (Kring and Sloan, 2010; Sloan et al., 2017). Consequently, understanding the neural underpinnings of ER, has become one of the most popular topics in affective neuroscience throughout the last two decades.

A very influential perspective in emotion theories is related to appraisal (Aldao and Tull, 2015; Sander et al., 2005; Scherer, 1984). Emotions arise in a person-situation context that draws attention to the emotional event. This attention binding implies a particular saliency of the event for the individual and in consequence leads to coordinated multi-system response tendencies (Gross, 1998). This multi-system responses have been proposed to rely on interacting, hierarchical neural systems that support the generation, perception and regulation of emotions (Smith and Lane, 2015). Along the emotion-generative process, different ER strategies have been distinguished such as distraction, reappraisal, and suppression (Gross, 2002; Webb et al., 2012). Distraction and reappraisal represent antecedent-focused strategies and aim to influence the generation and perception of an emotion before the emotion response tendencies have become fully activated. Distraction is a process in which selective attention is used to limit the extent to which the emotionally evocative aspects of an event or stimulus are attended and appraised, while reappraisal helps to alter the emotional impact of a stimulus/situation by e.g., reinterpretation, detachment, or perspective taking. (e.g., Kanske et al., 2011). In contrast, suppression represents a response-focused strategy and aims to alter the emotional

* Corresponding author at: Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Lazarettgasse 14, 1090 Vienna, Austria.
E-mail address: carmen.morawetz@meduniwien.ac.at (C. Morawetz).

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impact of a stimulus or event after a response tendency has already been generated and produces decreased expressive behaviour. Typically, suppression is used to inhibit behaviors associated with emotional responding with little or no change in ongoing emotion experience, for example, by modifying the facial expression (e.g., Goldin et al., 2008).

To investigate the regulation and also perception of emotions, a standard approach has evolved over the past two decades (Morawetz et al., 2017). An emotional stimulus – usually an aversive image – is presented and participants are either asked to down-regulate their emotions (regulation condition) by using a specific ER strategy (e.g., distraction (e.g., Kanske et al., 2011; Dörfel et al., 2014), reappraisal (e.g., Ochsner et al., 2004a,b; Silvers et al., 2015a), or suppression (e.g., Lévesque et al., 2003; Goldin et al., 2009)) or to look at the image and let themselves respond naturally (emotional viewing or perception condition; which is distinct from a neutral picture control condition). Using this approach, emotion generative processes can be dissociated from emotion regulatory processes (Gross et al., 2011) by contrasting the different conditions (McRae et al., 2012b; Ochsner et al., 2009; Otto et al., 2014). Emotion generation is investigated by the contrast of perception versus regulation condition or by emotional viewing versus neutral viewing, while emotion regulatory processes are targeted by contrasting the regulation versus control condition.

Previous studies linked emotion generation to an increase in brain activation of subcortical regions such as the amygdala (McRae et al., 2012b; Ochsner et al., 2009), while the control aspect of ER has primarily been linked to an increase in prefrontal cortex activation and a decrease in amygdala response (Banks et al., 2007; Johnstone et al., 2007; Urry et al., 2006). This has been interpreted in terms of dual opposing systems. However, recent models of emotion processing are incompatible with the notion of two systems and suggest that there are multiple neural circuits underlying emotion processing and ER (Barrett, 2017; Barrett and Satpute, 2013; Pessoa, 2008; Smith and Lane, 2015), which also supports the idea of the interacting linkage between emotion-generative and emotion-regulatory processes (Kappas, 2011; Thompson, 2011). However, this view commonly suggests that multiple neural systems interact in emotion perception and generation, which are modulated by and themselves influence regulatory systems. In terms of neural implementation, it is suggested that these systems rely on large-scale networks (Barrett, 2017; Bressler and Menon, 2010; Riedel et al., 2018; Sripada et al., 2014).

Several meta-analyses (Buhle et al., 2014; Frank et al., 2014; Kohn et al., 2014; Messina et al., 2015; Morawetz et al., 2017) summarized the findings of the ER literature and identified brain regions consistently activated during ER. These included lateral prefrontal cortex (dorsolateral and ventrolateral prefrontal cortices, DLPFC and VLPFC), somatosensory cortex (supplementary motor area, SMA), insula, amygdala, parietal and temporal regions. Multiple neural models of ER (e.g., Dixon et al., 2017; Etkin et al., 2015; Ochsner et al., 2012; Phillips et al., 2008; Silvers and Guassi Moreira, 2019; Smith and Lane, 2015) identified functional roles for each of these regions in various aspects of emotion perception, generation and regulation using reverse inference (i.e. infer the engagement of specific mental processes from patterns of activation) (Poldrack, 2011, 2006). Yet, these neural models of ER lack a data-driven, quantitative assessment of the psychological functions most likely underlying emotion-generative and emotion-regulatory processes.

Though conventional coordinate-based meta-analytic approaches (Eickhoff et al., 2009, 2012; Eickhoff et al., 2016a,b; Laird et al., 2005a,b; Turkeltaub et al., 2002) have been able to overcome the sensitivity limitations associated with individual fMRI studies, they have at least two important limitations with regard to their interpretation. First, conventional meta-analyses focus on regional contributions of brain regions during a specific task using a specific contrast. In ER this would be most commonly a comparison of reappraisal to down-regulate negative emotions in response to pictures from the International Affective Picture System [IAPS (Bradley and Lang, 2007)] to a control condition in which participants are asked to view the affective stimuli. While such an approach targets the specific aspect of regulation, it is not sensitive to the broader interactive process of ER embedded in a hierarchical organization of emotion perception, generation and regulation. Thus, it cannot inform the large-scale network-level perspective of emotion processing (Barrett, 2017; Bressler and Menon, 2010; Riedel et al., 2018; Sripada et al., 2014). Second, due to inferential limitations of conventional meta-analyses (Poldrack and Yarkoni, 2016) the specificity of brain-cognition associations i.e. the psychological processes underlying ER cannot be quantified. Therefore, we lack a model of psychological processes involved in ER that also maps systematically onto large-scale networks.

By using an established meta-analytic clustering technique (Bottenhorn et al., 2017; Flannery et al., 2020; Laird et al., 2015; Riedel et al., 2018) in the present study, we aimed to overcome firstly the limitation of not being able to segregate multicomponent processes and associated neural networks by tapping into subtle differences in the implementation of fairly standardized emotion regulation tasks and different strategies across a large body of studies. In the present study, we adopted a preferably broad conceptualization of cognitive control of emotions and included a variety of emotion regulation strategies (i.e., distraction, reappraisal, suppression) in combination with different regulation goals (i.e. up-regulation and down-regulation) and emotion induction methods (i.e. pictures, film clips, faces, reward, pain, and scripts) to determine and group over general neural circuits underlying emotion generation, perception and regulation processes. With this we want to answer the following key issues in the field of ER: First, which distributed brain areas operating in large-scale networks support emotion perception/generation and which underlie emotion regulation? Second, which psychological processes are associated with different large-scale networks activated during ER?

To address the first issue, we attempted to identify and characterize multiple neural circuits underlying emotion generation, perception, and regulation processes, leveraging an established meta-analytic clustering technique (Bottenhorn et al., 2017; Flannery et al., 2020; Laird et al., 2015; Riedel et al., 2018). In contrast to more traditional coordinate-based meta-analyses, which focus mostly on assessing convergence of one contrast (e.g., task > control condition) per study, the clustering method allows to investigate all possible contrasts (i.e. regulation task > emotional baseline; emotional baseline > regulation task; emotional baseline > neutral baseline; neutral baseline > emotional baseline; regulation task > neutral baseline; neutral baseline > regulation task) and determine in a data-driven fashion, which regions/networks of convergent activity can be identified across all contrasts and whether the resultant regions/networks are driven by certain contrasts. Using this technique, we parsed clusters of co-activation patterns reported across emotion regulation studies to detect large-scale brain-networks underlying different forms of emotion regulation. This clustering method should highlight discrete sub-networks related to differences in implementation of the tasks and regulation strategies across studies. To answer the second question, we quantified not only which kind of tasks tend to consistently produce activity in the clusters related to ER, but also which processes are associated with activity in a certain network. To characterize the functional associations of the resulting networks we used functional decoding of metadata terms (i.e. task-level descriptions and behavioral domains).

On the basis of existing neural models (Etkin et al., 2015; Ochsner et al., 2012; Phillips et al., 2008; Silvers and Guassi Moreira, 2019; Smith and Lane, 2015), we expected to determine at least three distinct whole-brain networks: The first network was hypothesized to be implicated in the top-down control of emotions and based upon fronto-parietal regions. The second one was anticipated to be involved in the perception and generation of emotions with the amygdala, striatum and anterior insula as key regions. A third network was expected to serve as a link between the first two networks with temporal, parietal, and medial prefrontal regions adopting an intermediary role. In addition,

we anticipated that numerous cognitive and affective processes will be associated with and important to ER. Previous research suggested that multiple cognitive processes like selective attention, working memory, response selection and inhibition, and conflict monitoring play a key role in ER. Similarly, motivational or affective aspects have been identified to influence ER, such as attribution of mental states, encoding of reward and arousal value of a stimulus, representation of body states related to emotions and representation of perceptual and semantic features (Ochsner et al., 2012). Additionally, recent theoretical accounts highlight other potential processes to be fundamentally involved in ER such as memory control (Engen and Anderson, 2018), language (Messina et al., 2015) and homeostasis/interoception (Barrett, 2017; Smith and Lane, 2015).

Collectively, the aims of the current study were threefold. We aimed to (1) provide a relatively broad and unbiased perspective on the neural mechanisms supporting ER by elucidating the topographically distinct brain networks that support the perception, generation and regulation of emotions and provide consensus specification of precise *a priori* regions-of-interest for future studies; (2) relate the determined clusters of co-activation patterns during emotion-generative and emotion-regulatory processes to brain-networks underlying prominent psychological functions and evaluate their specificity in relation to ER; and (3) assess the accumulated evidence of existing neural ER models, inform and extend their psychological conceptualization, and promote the development of new hypotheses.

2. Methods

2.1. Literature search and annotation

We examined previously published meta-analyses on emotion regulation, which included 93 studies from peer-reviewed journals (as of October 15th, 2015) and conducted an additional literature search using PubMed (www.pubmed.com) (by July 31st, 2017). We used the same combination of keywords as in the previous study (Morawetz et al., 2017): “emotion regulation”, “affective regulation”, “implicit emotion regulation”, “explicit emotion regulation”, “interpersonal emotion regulation”, “extrinsic emotion regulation, “intrinsic emotion regulation”, “reappraisal”, “suppression”, “distraction”, “detachment”, “labelling”, “affective labelling”, “reinterpretation”, “rumination”, “fMRI”, “neuroimaging”, “functional magnetic resonance imaging”, or “functional MRI”. This search revealed 85 studies. In the case that a study did not report the contrast of interest for this meta-analysis, the corresponding authors were contacted and asked to provide more information on their data. In the following the term “experiment” refers to any single contrast analysis, while the term “study” refers to a scientific publication, usually reporting several contrasts, i.e. experiments (Laird et al., 2011).

The inclusion criteria for articles were the following:

(1) We only included data from studies of healthy adults with no prior report of neurological, medical, or psychiatric disorders in the current meta-analysis, while results of patients or specific sub-group effects (e.g., sex differences) were not included. Articles including patients were only selected if they reported results for a control group separately, and only the latter group was included here.
(2) Only neuroimaging studies, which used whole-brain fMRI and reported coordinates for brain activation or deactivation in standard anatomical reference space (Talairach/Tournoux; Montreal Neurological Institute (MNI)) were considered. To address problems caused by different coordinates used in different studies, coordinates originally published in Talairach space were converted to MNI space using the algorithm implemented in GingerALE 2.3.5 (Laird et al., 2010, 2009; Lancaster et al., 2007).
(3) Only studies reporting whole brain analyses were included, while studies based on partial coverage or employing only region-of-interest analyses were excluded.

This search and the employed inclusion/exclusion criteria led to a total inclusion of 107 studies from peer-reviewed journals by July 31st, 2017 (385 experiments, 3204 participants) (Supplementary material, Table S1).

Each experiment was manually coded by two authors (CM & NK) with terms that described the experimental design with respect to contrast (e.g., regulation task > emotional baseline, emotional baseline > neutral baseline, etc.), stimulus type utilized (e.g., pictures, film clips, etc.), emotion regulation strategy (e.g., distraction, reappraisal), goal of the strategy (e.g., increase, decrease), valence of the stimuli (e.g., positive, negative), tactics of the strategy (reappraisal tactics according to McRae (McRae et al., 2012a) such as e.g. detachment, perspective taking, reality change etc.). The exact details on the manual annotations can be found in **2.3 Functional decoding** of meta-analytic groupings. These terms described the aspects of the stimuli and behaviors associated with each individual experimental contrast, thus focusing on the tasks of each modelled experimental contrast, and not the intended psychological construct underlying the original study report.

2.2. Analyses

The analysis followed a six-step approach, which has been established in previous studies (Laird et al., 2015; Riedel et al., 2018) (Fig. 1).

2.2.1. Generation of modelled activation (MA) maps (analysis step 1)

After identification of relevant studies and contrasts, reported three-dimensional coordinates in stereotactic space (x, y, z) of each study (only whole-brain statistical analysis) were extracted. This analysis step was not limited to specific experimental contrasts, which means that all experimental contrasts reported in a study were used in our analyses. More specifically, we included all possible combinations of task contrasts such as [regulation task > emotional baseline], [emotional baseline > neutral baseline], and [regulation task > neutral baseline] and vice versa. By implementing such an approach, we are able to determine in a purely data-driven way how distinct the resulting meta-analytic groupings (MAGs) are in terms of contributing statistical contrasts. Note, although, the resulting MAGs are spatially distinct and appear to correspond with dissociable psychological processes, different statistical contrasts can contribute to one MAG. In addition, this means that multiple contrasts from the same study are treated independently, such that each contrast has the opportunity to be classified into different clusters. This is especially important in the given context, such that different experimental manipulations within the same study produce distinct regions of brain activation. This is consistent with functional segregation and the flexible and complex nature of the experimental design, demonstrating that the manipulation of different contrasts can identify distinct networks that likely cooperate to successfully perform a complex task such as the cognitive control of emotions. Based on the coordinates of 385 experiments, probabilistic modelled activation (MA) maps were calculated from the foci reported in each individual contrast. To account for spatial uncertainty due to brain template and between-subject variance, the foci of each individual contrast were modelled as Gaussian kernels, with full width at half maximum determined by the number of subjects in each experiment (Eickhoff et al., 2009). The per-contrast FWHM varies by study sample size and in the present study ranged from 8.5215 mm to 10.0026 mm.

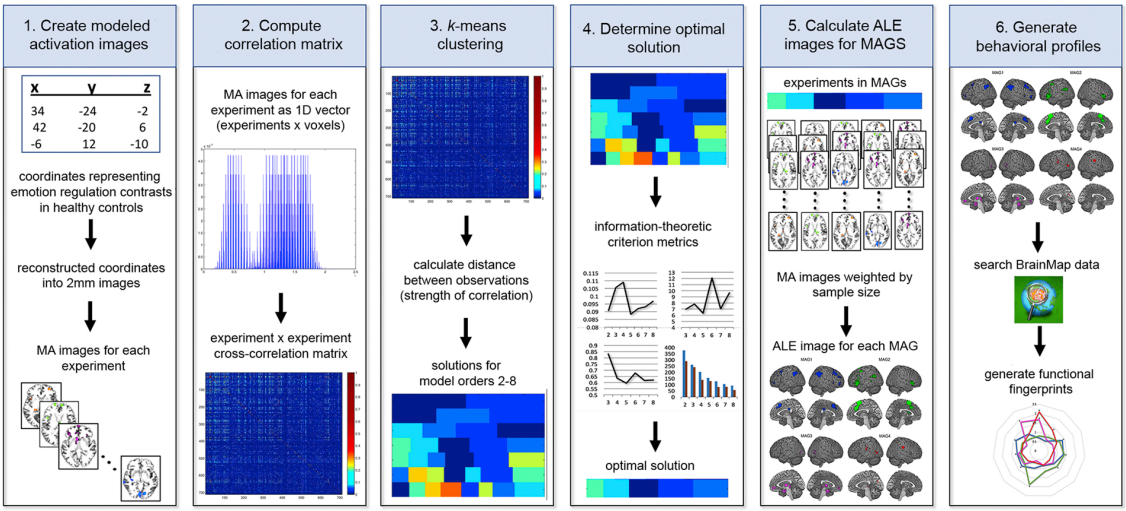

Fig. 1. Data extraction and *k*-means clustering analysis workflow, steps 1 through 6. Coordinates meeting inclusion criteria were reconstructed into activation maps (step 1). Each map was then collapsed to a one dimensional, experiment x voxel, vector. Pearson's correlations between every pair of experiment vectors generated an experiment x experiment cross correlation matrix (step 2). *k*-means clustering analysis grouped experiments based on 7 different model orders (2-8) (step 3). Four different metrics were used to determine the optimal clustering solution (step 4). Next, an activation likelihood estimation (ALE) meta-analysis ($p_{cluster\text{-}level} < 0.05$; $p_{voxel\text{-}level} < 0.001$) was run for each resulting meta-analytic grouping (MAG) to compute an ALE image of statistical correspondence (step 5). Finally, behavioural profiles were generated based on the BrainMap database (step 6).

2.2.2. Computation of correlation matrix (analysis step 2)

The resulting MA maps were concatenated into a one-dimensional array of *n* experiments by *p* voxels. In other words, each MA map of each experiment was represented in a vector. All vectors of all MA maps were concatenated into one matrix the size of experiments n and p voxels. Based on this matrix, a *n x n* symmetric cross-correlation (CC) matrix was calculated. The resultant Pearson correlation coefficient (*r*) between each pair of MA maps represented the similarity of spatial topography of MA maps between every possible pair of experiments.

2.2.3. k-means clustering analysis (analysis step 3)

In this step, *k*-means clustering analysis was performed on the CC matrix to determine MA maps with a similar activation pattern and parse them into meta-analytic groupings (MAGs). The *k*-means clustering procedure was performed in Matlab (Mathworks, R2013b for Linux), which grouped experiments by pairwise similarity, calculating correlation distance by 1 minus the correlation between MA maps (from the aforementioned correlation matrix) and finding the "best" grouping by minimizing the sum of correlation distances within each cluster. This approach begins by choosing *K* arbitrary maps as representative centroids for each of the *K* clusters and assigning experiments to each cluster based on the closest (most similar) centroid. This process continued iteratively until a stable solution was reached.

Solutions were investigated for a range of $K = 2$–8 clusters. Once the clustering analysis was complete for all *K*, we compared each solution with the neighboring solutions and assessed for improvement across parcellation schemes by using four metrics describing cluster separation and stability (Bzdok et al., 2015; Eickhoff et al., 2016a,b). This allowed us to objectively select the number of clusters that most optimally divided the dataset. The first metric, *average cluster silhouette* across clustering solutions, assessed how similar an experimental contrast's MA map is to other MA maps in its own cluster compared to MA maps in other clusters. A higher silhouette value indicates that greater separation is ideal and that each experiment fits well into its cluster, with lower misclassification likelihood of fringe experiments into neighboring clusters. Stability is indicated by a higher silhouette value compared to the $K - 1$ solution (primary criterion) or whose silhouette coefficient is at least not decreased compared to the previous $K - 1$ solution (secondary criterion). Second, we considered the *consistency of experiment assignment* by comparing the ratio of the minimum number of experiments consistently assigned to a cluster relative to the mean number of experiments consistently assigned to that cluster. In this case, only ratios above 0.5, in which at least half of the experiments were consistently assigned, were considered viable solutions. Third, the *variation of information* was quantified, which compared the entropy of clusters with the mutual information shared between them for each solution *K* and its $K - 1$ and $K + 1$ neighbors. A large increase from *K* to $K + 1$ (primary criterion) or decrease in variation of information from $K - 1$ to *K* (secondary criterion), a local minimum in the plot of variation of information across *K*, indicated a decrease in overlap between solutions and, thus, stability of solution *K*. In this case, "large" is defined, too, in relative terms, with the largest decrease indicating greatest stability of the solutions considered. Finally, we computed a *hierarchy index* for each solution, which assessed how clusters split from the $K - 1$ to *K* solution to form the additional cluster. A lower hierarchy index indicated that clusters present in *K* stemmed from fewer of the clusters present in $K - 1$, another indication of stability in groupings demonstrated by a hierarchy index lower than the median across all possible solutions and/or a local minimum across values of *K*. An optimal clustering solution is one that demonstrated minimal overlap between clusters (i.e., high silhouette value), while exhibiting relative stability in comparison with the previous and next solutions (i.e., consistency > 0.5, a local minimum in variation of information, and lower hierarchy index than previous).

2.2.4. Generation of activation-likelihood estimation (ALE) meta-analysis images (analysis step 4)

Following the application of a suitable clustering solution, convergent activation patterns within the MAGs were examined. To identify meta-analytic networks of activation across grouped experiments, we used the revised version (Eickhoff et al., 2012, 2009) of the activation likelihood estimation (ALE) algorithm for coordinate-based quantitative meta-analyses of neuroimaging results (Laird et al., 2005a; Turkeltaub et al., 2002). This algorithm aims to identify topographically overlapping clusters of activation across experiments within a single MAG that are significantly higher than expected compared to random spatial associations. The combination of all MA maps from all experiments was calculated to extract a voxel-wise ALE score that

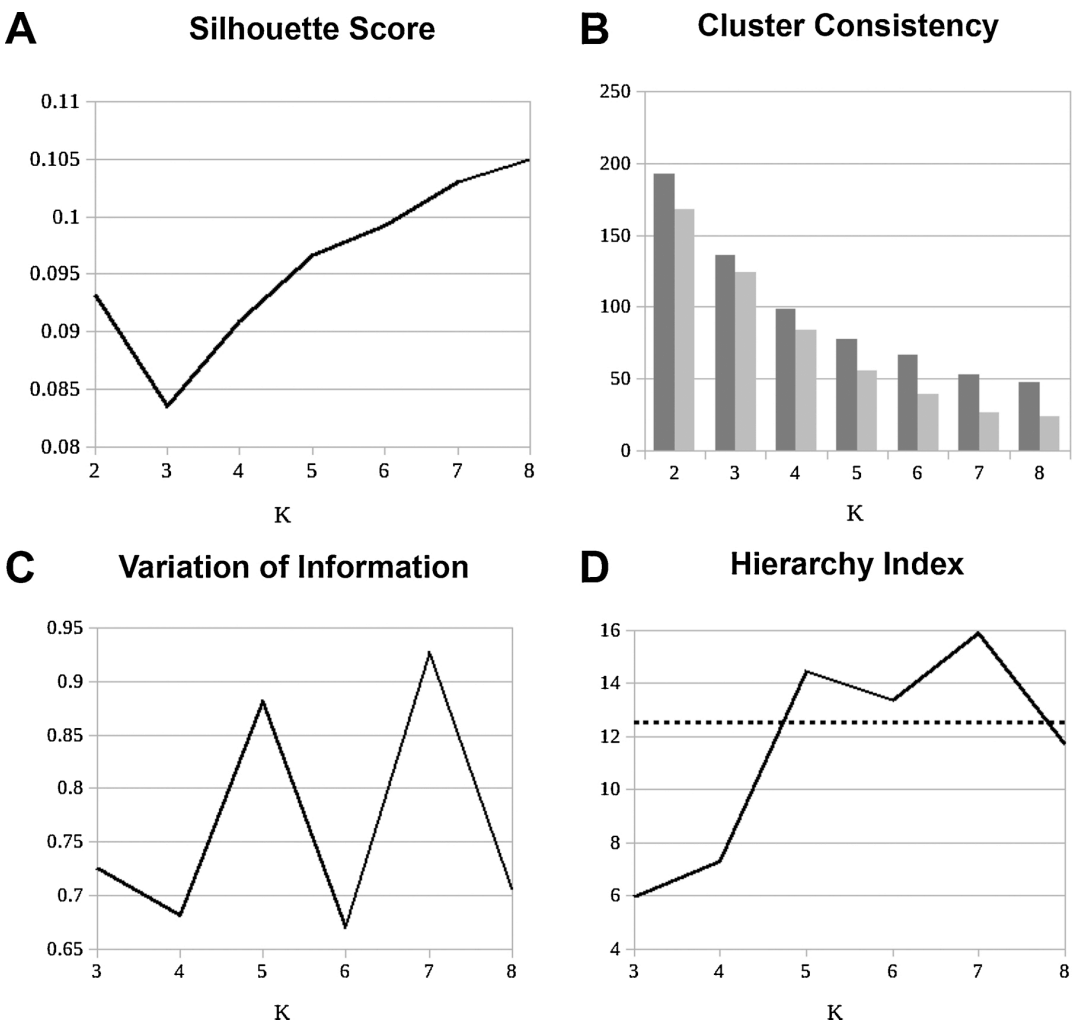

Fig. 2. *k*-means clustering solutions. **A** Average silhouette metric. **B** Consistency of assigned experiments metric. **C** Information metric. **D** Hierarchy index metric.

represented the convergence of results across experiments at each particular location in the brain. In order to distinguish 'true' convergence between studies from random convergence (i.e., noise), ALE scores were further compared to an empirical null-distribution, which represents a random spatial association between experiments (Eickhoff et al., 2012) and in which the same number of activation foci was randomly relocated and restricted by a gray matter probability map (Evans et al., 1994). In line with recent guidelines based on massive ALE simulations (EEickhoff et al., 2016a,b), ALE images were thresholded at a cluster-level corrected FWE threshold of $p_{cluster\text{-}level} < .05$ (cluster-forming threshold at voxel-level $p_{voxel\text{-}level} < .001$) (Eickhoff et al., 2012) as this represents the most appropriate method for statistical inference (Simon B Eickhoff et al., 2016a). For the anatomical labelling of the meta-analytic data probabilistic cytoarchitectonic maps provided in the SPM Anatomy Toolbox (Eickhoff, 2007; Eickhoff et al., 2006, 2005) were used. For visualization purposes, we used MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/home).

2.3. Functional decoding of meta-analytic groupings

2.3.1. Automatic BrainMap annotations

The functional characterization of the MAGs was based on the 'Behavioral Domain (BD)' and 'Paradigm Class (PC)' metadata categories available for each neuroimaging experiment included in the BrainMap database (Fox et al., 2005; Fox and Lancaster, 2002; Laird et al., 2009, 2005b). Behavioral domains include the main categories cognition, action, perception, emotion, and interoception, as well as their related sub-categories. Paradigm classes categorize the specific task employed (Turner and Laird, 2011) (see http://brainmap.org/scribe/ for the complete BrainMap taxonomy).

First, for each of the four MAGs the individual functional profile was determined by using the forward inference approach. This means, contrary to inferring mental function from brain activity ("reverse inference"), here we create a comprehensive mapping between data-derived taxonomic labels representing psychological states from the BrainMap database and the MAG's topography. Thus, forward inference is defined as the probability of observing activity in a brain region given knowledge of the psychological process. A MAG's functional profile was determined by identifying taxonomic labels, for which the probability of finding activation in the respective cluster was significantly higher than the overall chance (across the entire database) of finding activation in that particular cluster. Significance was established using a binomial test ($p < .05$, corrected for multiple comparisons using Bonferroni's method (Nickl-Jockschat et al., 2012; Rottschy et al., 2012)). That is, we tested whether the conditional probability of activation given a particular label [P(Activation|Task)] was higher than the baseline probability of activating the region in question per se [P(Activation)]. Significance (at $p < .05$, corrected for multiple comparisons

using Bonferroni's method) was then assessed by means of a chi-square test.

2.3.2. Manual annotations

Our manual annotations utilized a list of nine metadata categories, which captured salient features of the experimental design. We were especially interested in which terms contributed most to each MAG and thus, calculated the frequency of occurrence within each MAG. This highlighted, which terms described the largest number of experiments per MAG. To evaluate the relative contribution of each term per MAG, we controlled for the base rate by dividing each term's per-MAG count by the total of all contributing experiments per MAG. Thus, the results indicate the percentage of contribution of each term to the MAG.

Our manual annotation classified the included studies in terms of 'task' (i.e., regulation or reactivity), 'contrast' (i.e., regulation task > emotional baseline, emotional baseline > neutral baseline, regulation task > regulation task, regulation task > neutral baseline as well as reverse contrasts), 'strategy' (i.e., distraction, reappraisal, suppression), 'regulation goal' (i.e., decrease, maintain, increase), 'valence' of the stimuli (i.e., negative, positive, neutral), 'stimulus source' (e.g., visual, auditory, electrophysiological/physiological, verbal), 'stimulus category' (e.g., picture, film clips, other), 'stimuli' (e.g., IAPS, faces, pain, film, etc.), 'tactics' (e.g., detachment, perspective taking, etc.) and 'gender of participants' (i.e., female, male, both, difference). We were especially interested which terms contributed to each MAG and thus, calculated the frequency of occurrence within each MAG. To evaluate the relative contribution of each term per MAG, we controlled for the base rate by dividing each term's per-MAG count by the total of all contributing experiments per MAG. Thus, the results indicate the percentage of contribution of each term to the MAG. Of note, as tactics could not be determined for each study, related results are not reported.

3. Results

3.1. Large-scale brain networks in emotion regulation

Meta-analytic (MA) maps were created for each contrast and then clustered to identify groups with similar activation topographies. For completeness, the *k*-means clustering solutions for $K = 2–8$ clusters were quantitatively evaluated across four metrics to identify an optimal solution (Fig. 2). When considering the average silhouette metric (Fig. 2A), values generally increased as K increased with the largest increase from $K = 3$ to 4. With respect to the consistency of assigned experiments metric (Fig. 2B), all of the solutions $K = 2–6$ met the stability requirement whereby the minimum number of experiments included in any iteration of the solution was at least 50 % of the mean

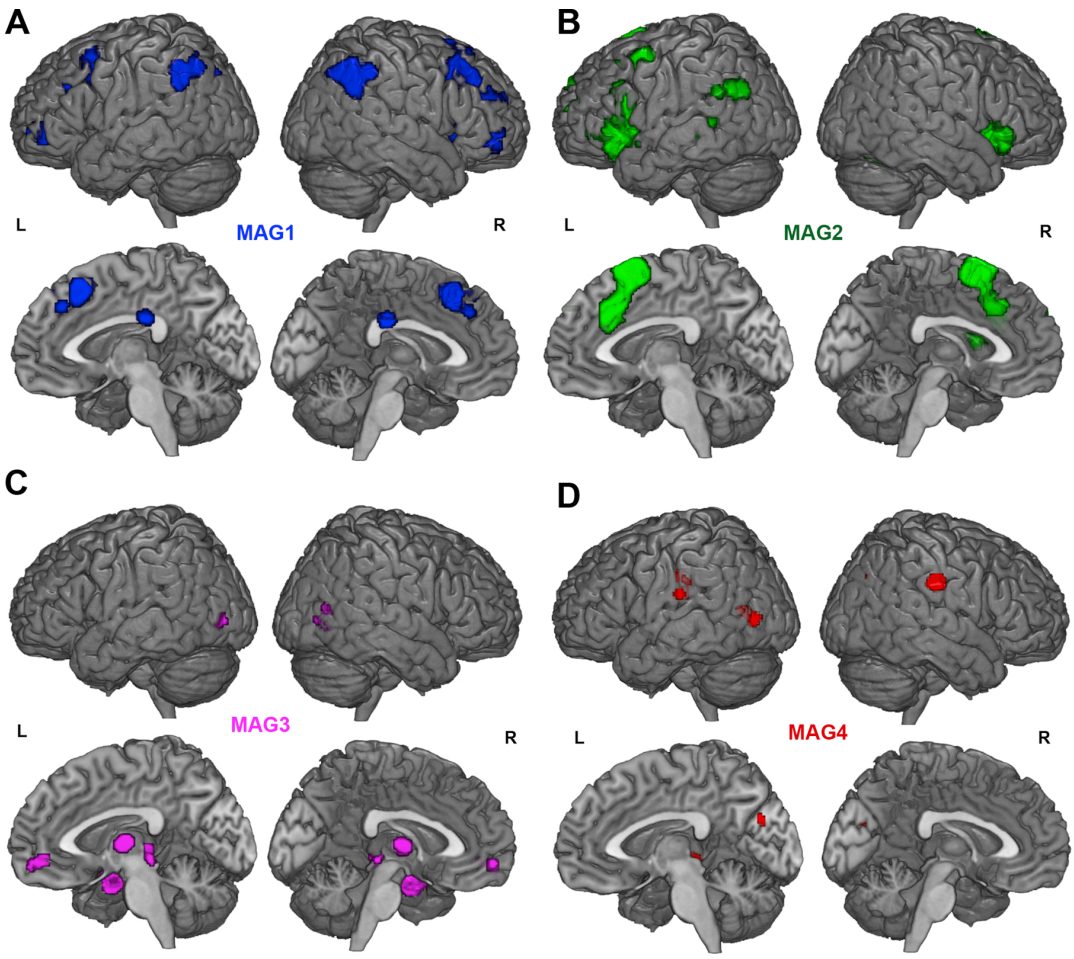

Fig. 3. Large-scale meta-analytic networks. Four meta-analytic groupings (MAGs) were identified. **A** MAG1 (indicated in blue) consisted of bilateral DLPFC and IPL, right insula, cingulate gyrus, precuneus, and SMA. **B** MAG2 (indicated in green) involved the bilateral VLPFC, left TPJ and middle temporal gyrus, SMA and left DLPFC. **C** MAG3 (indicated in purple) was based on bilateral amygdala and fusiform gyrus, left parahippocampal gyrus, PAG and VMPFC. **D** MAG4 (indicated in red) consisted of left SPL, bilateral postcentral gyrus, left insula, PAG, precuneus and PCC.

Table 1
MNI coordinates of ALE-derived meta-analytic groupings.

Meta-analytic grouping	Side	Region	BA	Volume	Coordinates x	y	z
1	L	Superior Frontal Gyrus	8	11704	0	24	50
	R	Middle Frontal Gyrus	8	11024	40	24	42
	R	Inferior Parietal Lobule	40	9968	58	−52	38
	L	Inferior Parietal Lobule	40	6216	−58	−50	44
	L	Middle Frontal Gyrus	10	4664	−36	52	−2
	L	Middle Frontal Gyrus	6	4288	−42	14	48
	R	Middle Frontal Gyrus	11	2792	42	46	−8
	R	Insula	13	2000	36	16	6
	R	Cingulate Gyrus	23	1336	2	−22	30
	R	Precuneus	7	944	10	−64	36
2	L	Inferior Frontal Gyrus	47	19464	−46	24	−8
	L	Superior Frontal Gyrus	6	16592	−4	10	62
	R	Inferior Frontal Gyrus	47	6856	50	28	−8
	L	Superior Temporal Gyrus	39	6704	−46	−52	28
	L	Middle Temporal Gyrus	*	5024	−54	−34	−2
	L	Middle Frontal Gyrus	6	4568	−44	6	50
	L	Superior Frontal Gyrus	9	3080	−30	48	26
	L	Caudate	*	1960	−16	10	12
	R	Tuber	*	1640	36	−60	−30
3	L	Amygdala	*	8640	−22	−4	−16
	R	Amygdala	*	6512	24	−4	−18
	R	Fusiform Gyrus	37	4776	40	−46	−18
	R	Thalamus	*	3528	6	−26	0
	L	Fusiform Gyrus	37	1256	−38	−54	−14
	L	Parahippocampal Gyrus	27	1216	−22	−28	−4
	B	Medial Frontal Gyrus	10	1016	0	54	−10
	L	Inferior Occipital Gyrus	19	912	−42	−76	−6
4	L	Postcentral Gyrus	2	4160	−58	−22	32
	L	Insula	13	3752	−44	−4	10
	L	Superior Parietal Lobule	7	2240	−28	−52	56
	R	Postcentral Gyrus	2	1736	62	−22	30
	L	Cuneus	18	1224	−10	−76	22
	L	Middle Occipital Gyrus	19	1152	−48	−74	2
	R	Thalamus	*	1024	10	−26	−4
	R	Precuneus	19	832	28	−60	38
	R	Posterior Cingulate	30	832	16	−56	16

Note. MAGs 1–4 were subjected to cluster-level FWE thresholding (pcluster-level < .05).
Peak cluster coordinates associated with each ALE map corresponding to the MAG are reported.
Side: L = left, R = right, B = bilateral.

number of experiments included across iterations. Solutions where K = 7, 8 resulted in clusters of experiments with smaller than half of the average number of experiments across clusters. The variation of information metric (Fig. 2C), suggested the stability of 4- and 6-cluster solutions as parameter value *decreases* were observed when moving from K = 3 to 4 and K = 5 to 6, respectively, combined with parameter *increases* when moving from K = 4 to 5 and K = 6 to 7, respectively, indicating that 4- and 6-cluster solutions demonstrate relative stability. The hierarchy index metric (Fig. 2D) further corroborated a 4-cluster solution, as it contained a hierarchy index quantity less than the median value across all possible solutions. Because of agreement across these metrics, we chose to proceed with the K = 4 solution.

3.2. Spatial topographies of best clustering solution

Based on agreement across the clustering metrics, ALE maps for each of the meta-analytic groupings (MAGs) for the four cluster solution were generated. Details on the four MAGs such as which studies and contrasts contributed to each MAG can be found in the Supplementary Material in Table S2.

The first MAG involved regions of convergent activation in the left superior frontal gyrus/dorsolateral prefrontal cortex (SFG/DLPFC), bilateral inferior parietal lobe (IPL), supplementary motor area (SMA) right insula, cingulate gyrus and precuneus (Table 1, Fig. 3A, MAG1 indicated in blue). The second MAG revealed convergent activation in bilateral inferior frontal gyrus/ventrolateral prefrontal cortex (IFG/VLPFC), left superior temporal gyrus/temporo-parietal junction (STG/TPJ), left middle temporal gyrus (MTG), left middle frontal gyrus (MFG), SMA and left caudate (Table 1, Fig. 3B, MAG2 indicated in green). Significant convergence in the third MAG was observed in bilateral amygdala, fusiform gyrus, left parahippocampal gyrus, medial frontal gyrus/ventromedial prefrontal cortex (VMPFC), periaqueductal grey (PAG) and inferior occipital gyrus (Table 1, Fig. 3C, MAG3 indicated in purple). Finally, the fourth MAG demonstrated convergent activation in bilateral postcentral gyrus, the left insula, the left superior parietal lobe (SPL), cuneus and precuneus, posterior cingulate cortex (PCC) and PAG (Table 1, Fig. 3D, MAG4 indicated in red).

3.3. Functional decoding of the four MAGs

To determine the functional and behavioral profiles of the spatially different MAGs, we used forward inference analyses. Fig. 4 illustrates BrainMap metadata terms with an above chance likelihood of reporting activity within areas of the MAGs. These unique metadata terms associated with individual MAGs help to interpret the cognitive, affective and perceptual processes specifically related to each MAG.

MAG1 consisted mainly of a fronto-parietal network including the DLPFC, which was associated with the cognition and action domain in the forward and reverse inference analyses of the metadata terms (Fig. 4). Within this MAG, paradigms involved in working memory, explicit memory, reasoning and inhibition were significantly represented.

MAG2 exhibited convergent activation in a left-lateralized prefrontal network including the VLPFC, which was primarily linked to the

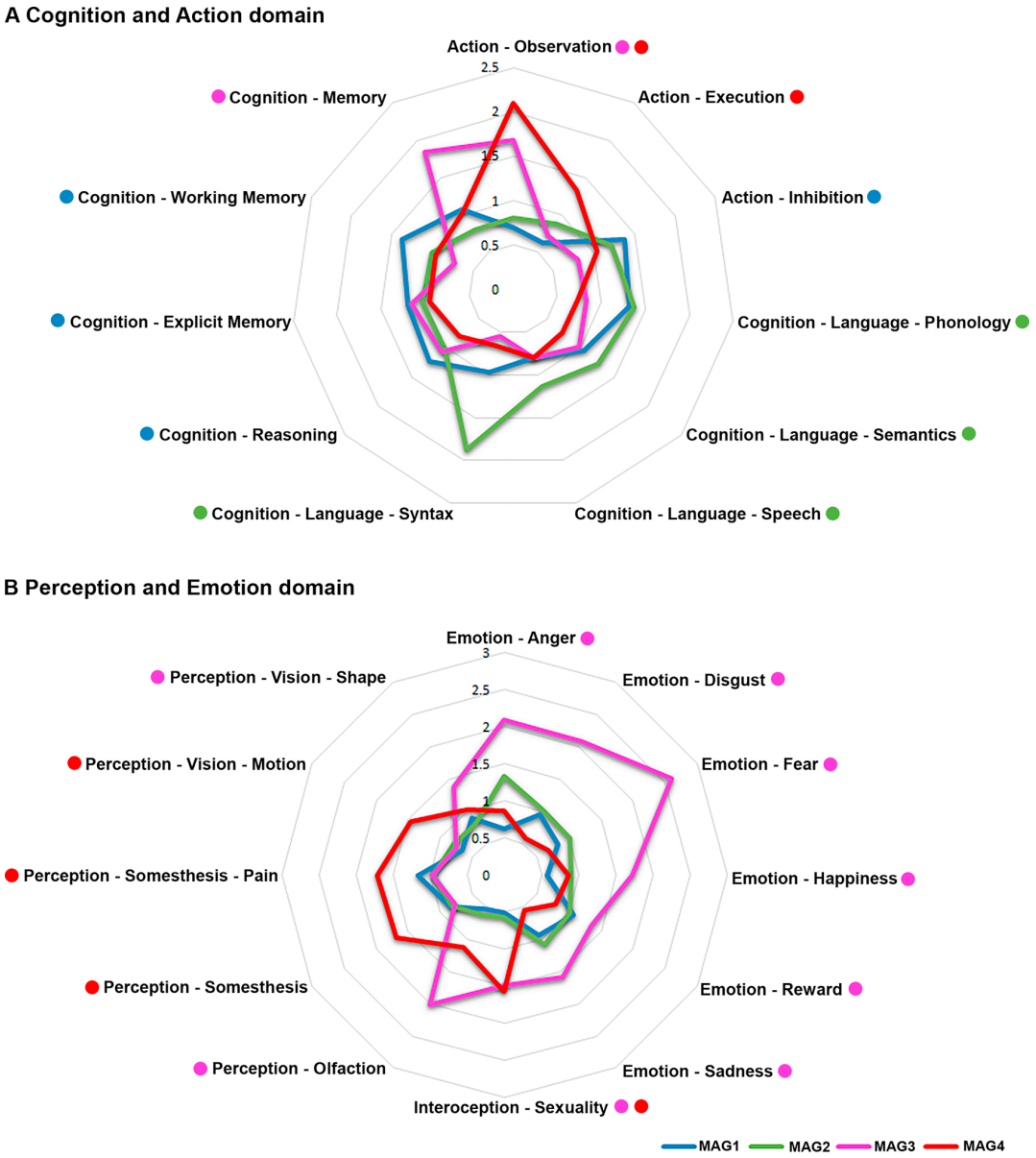

Fig. 4. Functional fingerprints associated with the four MAGs for **A** the cognition and action domain and **B** the perception and emotion domain. Each MAG was profiled to determine which psychological processes best predicted its activation. Displayed are terms significantly associated with the four MAGs (pFDR-corrected < 0.05). Significance is indicated next to each psychological concept by color-coded dots corresponding to each MAG.

cognition domain according to the analysis of metadata terms (Fig. 4). Paradigms related to language processes were significantly represented within this MAG.

MAG3 consisted of subcortical regions such as bilateral amygdala and left parahippocampus, bilateral fusiform gyrus, the VMPFC as well as the PAG. The analysis of metadata terms clearly indicated a focus on the emotion and memory domains (Fig. 4).

MAG4 was based on convergent activation in the insula, left SPL, PAG, precuneus and PCC, which was associated with the action, perception and interoception domain (Fig. 4). This activation pattern has been related to studies investigating motion, pain, somesthesis, and interoception.

3.4. Task-related analysis

In addition to these unique metadata terms, we were interested in the characteristics of the MAGs, i.e., which tasks, strategies, regulation goals, stimulus (valence, stimulus type) and sample features (e.g., gender) contributed the most to each MAG. Thus, we used the manual annotations assigned to each experiment to calculate the proportion of term occurrence for each MAG. The detailed results for all terms are reported in Table 2. Term frequency for task, strategy, regulation goal, valence, source of emotional input, stimulus category and gender are illustrated in Fig. 5. The joint evaluation of the metadata terms and the

Table 2
Manual functional decoding results across meta-analytic groupings (MAGs).

Term	MAG1		MAG2		MAG3		MAG4	
	n	%	n	%	n	%	n	%
Task								
Regulation	86	91	111	93	24	28	36	42
Reactivity	8	9	8	7	63	72	49	58
Contrast								
Regulation Task > Emotional Baseline	64	68	89	75	10	11	20	24
Emotional Baseline > Regulation Task	4	4	2	2	36	41	32	38
Regulation Task > Regulation Task	17	18	11	9	7	8	7	8
Regulation Task > Neutral Baseline	4	4	10	8	6	7	4	5
Neutral Baseline > Regulation Task	2	2	0	0	3	3	1	1
Emotional Baseline > Neutral Baseline	2	2	5	4	23	26	8	9
Neutral Baseline > Emotional Baseline	0	0	0	0	1	1	8	9
Other (mixed contrasts)	1	1	2	2	1	1	5	6
Strategy								
Reappraisal	65	69	97	82	19	22	28	33
Distraction	4	4	4	3	2	2	2	2
Suppression	7	7	1	1	0	0	2	2
Control (Maintain)	8	9	8	7	63	72	49	58
Other (e.g., Reappraisal > Distraction)	10	11	9	8	3	3	4	5
Goal								
Decrease	78	83	67	56	15	17	22	26
Increase	1	1	20	17	5	6	8	9
Maintain	8	9	8	7	63	72	49	58
Other (e.g., Increase > Decrease)	7	7	24	20	4	5	6	7
Valence								
Negative	63	67	106	89	70	80	66	78
Positive	8	9	7	6	6	7	2	2
Neutral	4	4	0	0	2	2	7	8
Mixed (e.g., Negative + Neutral)	19	20	6	5	9	10	10	12
Source								
Visual	91	97	112	94	80	93	76	89
Verbal	1	1	3	3	5	6	4	5
Electrophysiological/Physiological	2	2	3	3	1	1	3	4
Other (e.g., visual + verbal)	0	0	1	1	0	0	2	2
Stimulus category								
Picture	78	83	88	74	74	85	61	72
Film	10	11	16	13	6	7	10	12
Film + Picture	1	1	4	3	0	0	0	0
Other (e.g., scripts, money/reward, pain)	5	5	11	9	7	8	14	16
Gender								
Female	31	34	30	26	28	33	16	19
Male	0	0	2	2	0	0	2	2
Both (female and male)	58	64	85	73	55	65	63	75
Difference (e.g., female > male)	2	2	0	0	1	1	3	4

Note. N = total number of term frequency. % The relative contributions of each manually derived metadata term (i.e., term frequencies) were computed for all MAGs, controlling for the base rate by dividing each term's per-MAG count by the total number of experiments in each MAG.

manual annotations allowed the generation of functional and behavioral profiles for each MAG.

For MAG1, the analysis of task indicated an emphasis on task instructions related to emotion regulation, i.e., 91 % of the experiments that contributed to MAG1 were linked to the regulation phase (mainly contrasting emotion regulation > emotional baseline [68 %] or contrasting two regulation conditions with each other [18 %]) (Table 2, Fig. 5A). The experiments that contributed most to the first MAG implemented reappraisal as regulation strategy [69 %] with the goal to down-regulate [83 %] negative emotions [67 %] in response to emotional pictures [83 %] and film clips [11 %].

In MAG2, the examination of task contribution yielded a clear association with the emotion regulation phase with 93 % (mainly implementing the contrast of emotion regulation > emotional baseline [75 %]) (Table 2, Fig. 5B). Similar to MAG1, the second MAG was mostly driven by reappraisal [82 %] with the goal to down-regulate [56 %] and also up-regulate [17 %] negative emotions [89 %] in response to pictures [74 %] and film clips [13 %]. Together, these findings indicate that the first and second MAG are linked to the regulation of emotional responses by using reappraisal.

In contrast to the first two MAGs, we found that 72 % of the experiments tested for the reverse condition, namely, for emotional reactivity i.e. emotion perception/generation in MAG3 (mainly contrasting the emotional baseline > emotion regulation [41 %] and emotional baseline > neutral baseline [26 %]) (Table 2, Fig. 5C). Thus, most experiments implemented a task design with the control condition as strategy [72 %] in order to maintain [72 %] the emotional response when viewing negative [80 %] pictures [85 %]. This suggests that the third MAG is primarily involved in memory-related emotion processing and emotion generation.

MAG4 provides the most strongly mixed terms compared to the other MAGs (Table 2, Fig. 5D). The tasks that contribute to this MAG are related to the regulation phase [42 %] as well as emotional reactivity [58 %]. Thus, MAG4 is based on contrasts of emotion regulation > emotional baseline [24 %] and vice versa [38 %]. This also relates to the task designs implementing both, the reappraisal [33 %] as well as the control condition [58 %] with the goal to decrease [26 %] or maintain [58 %] the negative emotional responses [78 %]. Interestingly, the experiments contributing to MAG4 implement a more diverse range of stimuli such as pictures [72 %], film clips [12 %] and other stimuli [16 %] (i.e. electrophysiological stimulation, money/reward, faces, sentences, scripts, memories and pain). Thus, the fourth MAG

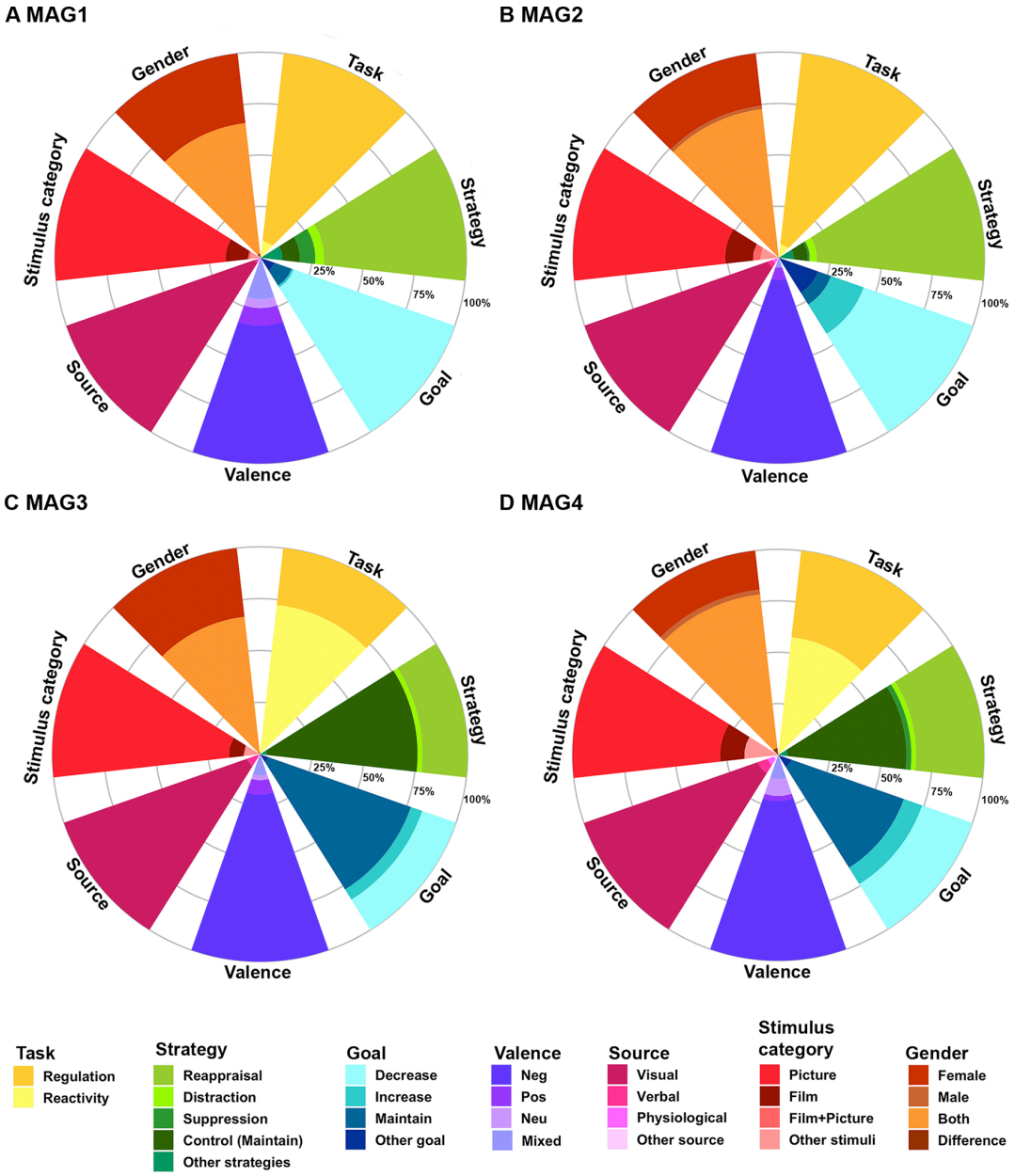

Fig. 5. Distribution of manual annotations/specific metadata terms, which captured salient features of the experimental design across MAGs (**A - D**). These percentages represent the proportion of terms within each metadata category present in each MAG.
Task (yellow): regulation (contrasts: [regulation task > emotional baseline]; [regulation task > regulation task]; [regulation task > neutral baseline]), reactivity (contrasts: [emotional baseline > regulation task]; [neutral baseline > regulation task]; [emotional baseline > neutral baseline]; [neutral baseline > emotional baseline]).
Strategy (green): Reappraisal, Distraction, Suppression, Control (Maintain), Other strategies (contrasts: [Reappraisal > Distraction]; [Distraction > Reappraisal]; [Suppression > Reappraisal]; [Reappraisal > Suppression]; [Reappraisal + Distraction + Suppression]; [Reappraisal + Distraction]).
Goal (blue): Decrease, Increase, Maintain, Other goal (contrasts: [Decrease > Increase]; [Increase > Decrease]; [Decrease + Increase]).
Valence (violet): Negative (Neg), Positive (Pos), Neutral (Neu), Mixed ([Neg + Neu], [Neg + Pos], [Neg + Pos + Neu]).
Source of input (pink): Visual, Verbal, Physiological, Other source ([Visual + Verbal]; conditioned stimulus).
Stimulus category (red): Picture, Film, Film + Picture, Other stimuli (scripts; money/reward; pain; faces/sentences; sentences/memories; e-shock).
Gender of the participants (orange): Female, Male, Both (female and male), Difference (contrasts: [female > male]; [male > female]).

seems to be involved in the perception of the emotional stimulus during the emotion generative process, and potentially also during the regulation of emotional responses.

Gender differences in emotional responding constitute one of the most robust stereotypes (Hess et al., 2000; Plant et al., 2000; Timmers et al., 2003). The preconception is that women are more emotional than men. Thus, early studies on emotion regulation only tested women (e.g., Eippert et al., 2007; Goldin et al., 2008; Kim and Hamann, 2007; Ochsner et al., 2004a,b, 2002) and few studies tested for gender differences (e.g., Mak et al., 2009; McRae et al., 2008). Therefore, in

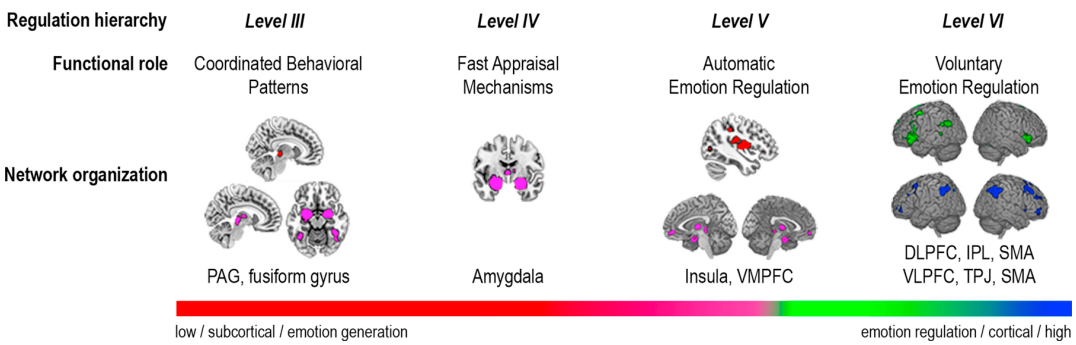

Fig. 6. Illustration of the association between the determined MAGs and the distinguishable levels of hierarchical regulatory control (adapted from Smith & Lane (Smith and Lane, 2015)).

addition, to the above-described characteristics of the MAGs, we examined whether the gender of the participants represents a key-contributing feature in the constitution of the MAGs. The experiments contributing to MAG1 and MAG3 show similar distributions for gender with 34 % and 33 % of the experiments only using a female sample and 64 % and 65 % of the experiments using a mixed sample (i.e. male and female participants), respectively. 73 % and 75 % of the experiments contributing to MAG2 and MAG4 were based on mixed samples, respectively, while the remaining 26 % and 19 % were allocated to experiments focusing on a female sample. Taken together, these findings suggest that the observed patterns of convergent activity within the MAGs might be independent of gender.

4. Discussion

In this study, we identified large-scale neural networks underlying emotion generation, perception and regulation based on convergent brain activation patterns reported during ER via data mining of 385 experiments from 107 published papers. We present empirical evidence for the idea of a multi-component view of ER supported by large-scale brain networks. We not only define the spatial topology of these networks but also present an empirically based qualitative label for the associated psychological processes. Using a meta-analytic k-means clustering approach and functional decoding analyses (Bottenhorn et al., 2017; Flannery et al., 2020; Laird et al., 2015; Riedel et al., 2018) we identified four distinct networks and associated psychological processes. Taken together, we observed two cortical networks that are mainly implicated in regulation (MAG1 and MAG2), one subcortical network that is associated with emotion perception and generation (MAG3), and one network that is linked to both, emotion regulatory processes as well as emotional reactivity (MAG4). The behavioral profiles associated with the distributed large-scale networks give rise to the assumption that these brain networks play different roles within the ER process. Overall, a convergent pattern for an experimental design to study emotion regulation emerged across the four networks. The observed MAGs were mainly based on experiments using reappraisal to down-regulate emotions in response to negative pictures. This represents a standard approach in emotion regulation research, which implies the advantage of a very homogenous set of data, but at the same time limits the possibility to determine differences between regulation strategies, regulation goals, stimulus type and features (Morawetz et al., 2017). Our results yield new insight into the multicomponent process of ER and provide a coherent framework for studying the functional architecture of ER.

The first two networks consisted of mostly lateralized cortical brain regions. These brain regions are nearly exclusively linked to the cognition domain in the BrainMap database. Based on the behavioral profile and network topology, we assume these two networks support mainly the regulatory process important for the reappraisal of negative stimuli to down-regulate their negative impact. Interestingly, the two regulatory networks are dissociated along a dorsal-ventral gradient, which has been discussed in the ER literature previously (Morawetz et al., 2016; Ochsner et al., 2012; Ochsner and Gross, 2005). The lateral dorsal PFC network (MAG1) is associated with working memory and response inhibition, while the lateral ventral PFC network (MAG2) is implicated in language processing. Such an association between topology and function has been previously proposed (Aron et al., 2004; Gazzaley and D'Esposito, 2007; Messina et al., 2015; Miller and Cohen, 2001; Ochsner et al., 2012; Thompson-Schill et al., 2005; Wager and Smith, 2003) and our results nicely corroborate some of these previous hypotheses.

Conversely, the other two networks include mainly subcortical brain regions and are most strongly linked to the perception and emotion domain in the BrainMap database. MAG3, the network including the amygdala, parahippocampus and VMPFC, is strongly associated with the perception of different emotional qualia and therefore seems to play a central role in emotional reactivity and the generation of emotional responses and potentially also the appraisal of emotional stimuli. MAG4 is implicated in emotion generation as well as regulation, yet represents the perception of internal sensations and thus is linked to interoception, body awareness, sensory predictions and somesthesis more strongly. Thus, MAG4 might serve as a hub that plays an intermediary role in reappraisal and integrates information from the prefrontal networks (MAG1 and MAG2) as well as the subcortical network (MAG3) in order to generate emotional responses on the one hand, and regulate these responses on the other hand. This is in accordance with the recently proposed model of constructed emotions which assumes that interoception is at the core of the brain's internal model (Barrett, 2017). MAG3 and MAG4 overlap in one region, the PAG, which might serve as a hub that is critical for regulating the flow and integration of information between the two networks. The PAG represents a highly connected brain region with connections to the descending limbic system and to the ascending sensory system, thus being involved not only in emotion processing but also in the integration of emotional aspects of homeostatic regulation via the automatic nervous system (Linnman et al., 2012).

Our findings map well onto the six-level regulation hierarchy proposed by Smith & Lane (Smith and Lane, 2015) to regulate emotions (Fig. 6). This model suggests a large-scale brain network organization in six levels which support emotion regulation. Our results nicely match four of these hierarchical levels and their respective psychological processes. Due to limitations of spatial resolution of whole-brain fMRI, SNR in brainstem regions and potentially also limits of temporal resolution of the HRF, we are not able to determine the lowest levels of body state- and behavioral-regulation at the somatic and visceral level (first level) as well as homeostatic regulatory control based on the subnuclei of the brainstem (second level) in our study. However, the third level of regulatory control that involves discrete body state

representations and perception of relevant stimuli partly matches to MAG4. One main region that appears to play a significant role within this regulation stage is the PAG, which we find in MAG3 and MAG4. Note, however, that the hypothalamus was not part of MAG4, which plays a significant role in addition to the PAG. The fourth level of regulation is generally associated with fast, automatic appraisal mechanisms. The amygdala is important for detecting and evaluating an emotional stimulus in a relevant situation (Adolphs, 2010, 2002) and for computing the salience of the stimulus (Ray and Zald, 2012). As the amygdala features strongly in MAG3 we attribute fourth-level regulation processes to this large-scale brain network. The fifth level of regulation integrates the interoceptive perceptual representations, assesses the current internal emotional state, and tracks the actual physiological changes (Craig, 2003; Stern et al., 2017; Wiens, 2005) in the insula (MAG4). Furthermore, it has been suggested that the VMPFC (MAG3) represents stable, high-level, contextually modulated appraisals, thereby generating “affective meaning” (Smith and Lane, 2015). Finally, on the highest level of regulation - voluntary ER (level 6) - the two cortical large-scale networks (MAG1 and MAG2) come into play. In sum, we propose that the distinguishable levels of hierarchical regulatory control are based upon dissociable yet interacting large-scale networks.

Our findings provide a coherent framework of multiple large-scale networks involved in the generation and regulation of emotions. Firstly, we present empirical evidence for organization in large-scale brain networks that not only spatially corroborate previous assumptions but also overlap with supposed association to psychological processes. Our findings may inform future network-based imaging analyses. Connectivity analyses between the cortical and subcortical networks that we have identified, such as the prefrontal regions and structures like the amygdala and PAG, may yield new insights into emotion regulation/dysregulation differences between populations (Nicholson et al., 2017). Thus, these networks provide an *a priori* selection of brain regions to model the causal direction of the effective connectivity between and within them. Specifically, the psychological profiles of each network provide the opportunity to test whether and which psychological processes can be trained to enhance ER ability. This could inform existing training programs for ER and thus, could potentially have particularly relevant applications in clinical work, such as for the intervention of anxiety disorders and depression.

5. Conclusion

We present evidence for large-scale brain network organization in emotion regulation that aligns well with the proposed regulation hierarchy (Smith and Lane, 2015). Regulatory networks are dissociated along a ventral-dorsal axis. They are functionally characterized by a stronger focus on response inhibition or executive control versus appraisal or language processing. The latter could be at the heart of reappraisal as prominent regulation technique. We identified one network that mainly relates to emotion generation and appraisal, and one network that is involved in basic physiological processes. Our findings corroborate and inform contemporary models of emotion regulation and thereby significantly add to the literature. We further provide behaviorally enriched large-scale brain network maps that can be used in future studies to deepen the understanding of the neural mechanisms supporting the generation and cognitive control of emotions.

Declaration of Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.07.001.

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