Different functions in the cingulate cortex, a meta-analytic connectivity modeling study

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Different functions in the cingulate cortex, a meta-analytic connectivity modeling study

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A B S T R A C T

The cingulate cortex is a structurally heterogeneous brain region involved in emotional, cognitive and motor tasks. With the aim of identifying which behavioral domains are associated with the activation of the cingulate cortex, we performed a structure based-meta-analysis using the activation likelihood estimation (ALE), which assesses statistical significant convergence of neuroimaging studies using the BrainMap database. To map the meta-analytic coactivation maps of the cingulate cortex (MACM), we subdivided the parenchyma along the rostro-caudal axis in 12 bilateral equispaced ROIs. ROIs were not chosen according to previously suggested subdivisions, as to obtain a completely data-driven result. Studies were included with one or more activation coordinates in at least one of the 12 pre-defined ROIs. The meta-analytic connectivity profile and behavioral domains profiles were identified for each ROI. Cluster analysis was then performed on the MACM and behavioral domains to group together ROIs with similar profiles. The results showed that the cingulate cortex can be divided in three clusters according to the MACM parcellation and in four according to the behavioral domain-based parcellation. In addition, a behavioral-domain based meta-analysis was conducted and the spatial consistency of functional connectivity patterns across different domain-related ALE results was evaluated by computing probabilistic maps. These maps identified some portions of the cingulate cortex as involved in several tasks. Our results showed the existence of a more specific functional characterization of some portions of the cingulate cortex but also a great multifunctionality of others. By analyzing a large number of studies, structure based meta-analysis can greatly contribute to new insights in the functional significance of brain activations and in the role of specific brain areas in behavior.

Introduction

Ever since the very first neuropsychological studies, researchers have attempted to relate behavioral functions to specific brain locations. Over the last three decades, research has produced an enormous amount of data localizing putative brain underpinnings of specific mental operations. Thus, given the impressive body of evidence at our disposal, the need of converging evidence among studies within a coherent theoretical framework is of primary interest.

The cingulate cortex is a particularly interesting area given the wide variety of tasks in which it is involved. Important information regarding the structure of this region and the functions it supports have been mainly obtained from non-human primates (Vogt and Pandya, 1987; Vogt et al., 1987); but see (Cole et al., 2009) for a discussion of the differences between human and non human primates. Despite the human cingulate cortex has been studied for over a century, its structural and functional organization remain debated. Four sub-regions have been proposed to constitute the cingulate cortex: the anterior (24/32), mid (24′/32′) posterior (23/31) and retrosplenial (23′/31′) cingulate cortex (Fan et al., 2008; Palomero-Gallagher et al., 2008; Palomero-Gallagher et al., 2009; Vogt, 2005). Each of these subdivisions is proposed to differ in terms of cytoarchitecture, connectivity and function. Moreover, considering the plethora of functions performed by the cingulate cortex, it is not surprising that functional resonance imaging (fMRI) studies are replete with activations of this area.

Anatomically, the anterior cingulate cortex is the more rostral part and the complexity of its functional connectivity has been well described (Koski and Paus, 2000; Margulies et al., 2007). The anterior cingulate cortex is central to a broad array of cognitive, sensory-motor, affective and visceral functions (Devinsky et al., 1995; Dum and Strick, 1991; Shima and Tanji, 1998; Vogt et al., 1995). For example, the anterior cingulate cortex is involved in conflict monitoring (Botvinick et al., 2004; Carter et al., 1998), error monitoring and detection (Gehring and Fencsik, 2001; Gehring and

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Abbreviations: ROI, region of interest; ALE, Activation likelihood estimation; MACM, Meta-analytic connectivity modeling.

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Knight, 2000; Holroyd et al., 1998; Lorist et al., 2005), response selection (Awh and Gehring, 1999; Paus et al., 1993) and attention control (Crottaz-Herbette and Menon, 2006; Posner and Dehaene, 1994). This functional heterogeneity is also reflected at the anatomical level, where the anterior cingulate cortex can be further subdivided in several distinct subregions (Devinsky et al., 1995; Vogt et al., 1995). However, it is worth noting that factors such as stimulus presentation rate (Bench et al., 1993), stimulus novelty (Petersen et al., 1998) and practice effect (Kelly and Garavan, 2005; Milham et al., 2003), also influence the activation of this portion of the cingulate cortex. Several lines of evidence from functional imaging and lesion studies suggest a broad division of the anterior cingulate cortex into dorsal and ventral areas (Bush et al., 2000; Koski and Paus, 2000; Yucel et al., 2003). The dorsal portion of the anterior cingulate cortex has been found to be strongly associated with motor, attentional and cognitive functions (MacDonald et al., 2000), whereas the ventral portions of such region (rostral, subcallosal and subgenual regions) seem to be involved in emotions, mood and autonomic functions (Mayberg et al., 2002).

The dorsal mid-cingulate cortex is central to skeletomotor regulations (Vogt et al., 1992), but its role in cognitive tasks has also been found repeatedly. Such cognitive tasks include: attention for action (Badgaiyan and Posner, 1998; Pardo et al., 1990), response selection (Corbetta et al., 1991; Paus et al., 1993), error detection and competition monitoring (Carter et al., 1998), anticipation (Murtha et al., 1996) and working memory (Petit et al., 1998).

The posterior cingulate cortex is thought to play an important role in tasks related to visuospatial orientation and navigation of the body in environmental space (Vogt and Laureys, 2005). Furthermore, its role has been identified in tasks related to self-reflection and autobiographical memory (Spreng et al., 2009).

Finally, the retrosplenial cingulate cortex seems to be involved in memory and visuospatial functions (Burgess et al., 2001; Iaria et al., 2007; Keene and Bucci, 2008; Parker and Gaffan, 1997; Vann et al., 2009; Vogt and Laureys, 2005; Vogt and Pandya, 1987; Vogt et al., 1987).

In the present study, we employed the meta-analytic connectivity modeling (MACM) (Robinson et al., 2010) to investigate the functional connectivity and the behavioral domains wherein the cingulate cortex has been found active. The MACM is based on the assumption that groups of coordinates that co-activate across experiments can be pooled to identify functionally connected networks. Like other methods of analysis of functional connectivity, analyses carried out which such a method are based on the co-occurrence of spatially separated neurophysiological events (Koski and Paus, 2000; Postuma and Dagher, 2006; Toro et al., 2008). The MACM allows structure-based meta-analyses, which instead of pooling studies that share a common experimental design, look for global co-activation patterns across a diverse range of tasks, thus responding to the question ‘for a given region what tasks elicit activation?’ (Laird et al., 2009b).

To retrieve areas co-activated by different studies we employed the BrainMap database (Laird et al., 2005). BrainMap is a community accessible database, which archives peaks coordinates from published neuroimaging studies, along with the corresponding metadata that summarize the experimental design. As suggested by Price and Friston (Price and Friston, 2005) the relationship between a brain region and a mental function is not one-to-one. Instead, a single region can be involved in many cognitive processes and single processes can activate multiple regions. To map the specific MACM of each part of the cingulate cortex we defined twelve $10\times10\times10$ mm bilateral ROIs along its rostral–caudal axis and examined the co-activations of these areas with other areas in the brain, using an activation likelihood estimation (ALE) approach. Successively, we identified the behavioral domains associated with each ROI. This subdivision in regions of equal size enabled the data-driven clustering of functional co-activations. A different choice, such as *a priori* defined anatomical subdivision would have prevented this data-driven or bottom-up approach.

Methods

Definition of the ROIs

The selection of the ROIs was not based on pre-existing subdivisions (anatomical, functional and histological) in order not to assume an *a priori* hypothesis; instead, our approach aimed at obtaining data-driven results. Therefore we selected 12 consecutive bilateral ROIs of $10\times10\times10$ mm along the rostral–caudal axis of the cingulate cortex (see Fig. 1 and Table 1). This choice was also motivated by the technical constraints of the MACM for which: i) a consistent number of foci is needed for each subdivision, ii) a comparable number of foci is needed in each voxel. The ratio between the minimal dimension of voxels we could select with such constraints and the dimension of the cingulate cortex led us to the identification of 12 subdivision.

Structure-based meta-analysis (Meta-analytic connectivity modeling, MACM)

MACM of regional co-activations was designed to establish connectivity patterns for task-related increases for each of the 12 ROIs. To analyze the whole-brain meta-analytic connectivity of the cingulate cortex, for each ROI we queried the BrainMap database for studies that included at least one or more activation coordinates in that ROI. Searches were conducted to find all experiments that reported activations in these regions during task conditions.

Activation likelihood estimation (ALE) meta-analysis

The Activation likelihood estimation (ALE) analysis is a quantitative voxel-based meta-analysis method which can be used to estimate consistent activation across different imaging studies (Laird et al., 2009a). ALE maps of co-activations are derived on the basis of foci of interest, where multiple studies have reported statistically significant peaks activation. Different formulations of the ALE have been proposed, in this study we used the Eickhoff and colleagues' (Eickhoff et al., 2009) one.

In the original formulation (Turkeltaub et al., 2002), activation likelihood estimates were calculated for each voxel by modeling each coordinate with an equal weighting using a 3-D Gaussian probability density function. Successively, a permutation test was carried out to determine the voxel-wise significance of the resulting ALE values. The permutation testing was implemented using a non-parametric statistical approach (Turkeltaub et al., 2002), in which usually 5000 or more permutations were generated using the same number of foci and Full Width at Half Maximum (FWHM) algorithm was used to generate the ALE map. As such, no assumptions were made with respect to the distribution or spatial separation of these random foci (Laird et al., 2005; Turkeltaub et al., 2002). Resulting statistical maps were corrected for multiple comparisons using false discovery rates (FDR), and then thresholded at $p<0.05$, corrected.

In the revised algorithm (Eickhoff et al., 2009), to limit the inter-subject and inter-laboratory variability typical of neuroimaging studies, an algorithm was implemented, which estimates the spatial uncertainty of each focus and takes into account the possible differences among studies. This algorithm was preferred to a pre-specified FWHM as in the original ALE approach (Turkeltaub et al., 2002). The advantage of the second algorithm is that it allows calculating the above-chance clustering between experiments (i.e., random effects analysis, RFX), rather than between foci (fixed effects analysis, FFX) (Eickhoff et al., 2009). Moreover, from the original ALE method (Turkeltaub et al., 2002), several other modifications have been applied. A cluster analysis script was added to identify areas of high activation likelihood and return the cluster extent above a user-specified threshold (Lancaster et al., 2005). Laird and colleagues also added a correction for multiple comparisons and a method for

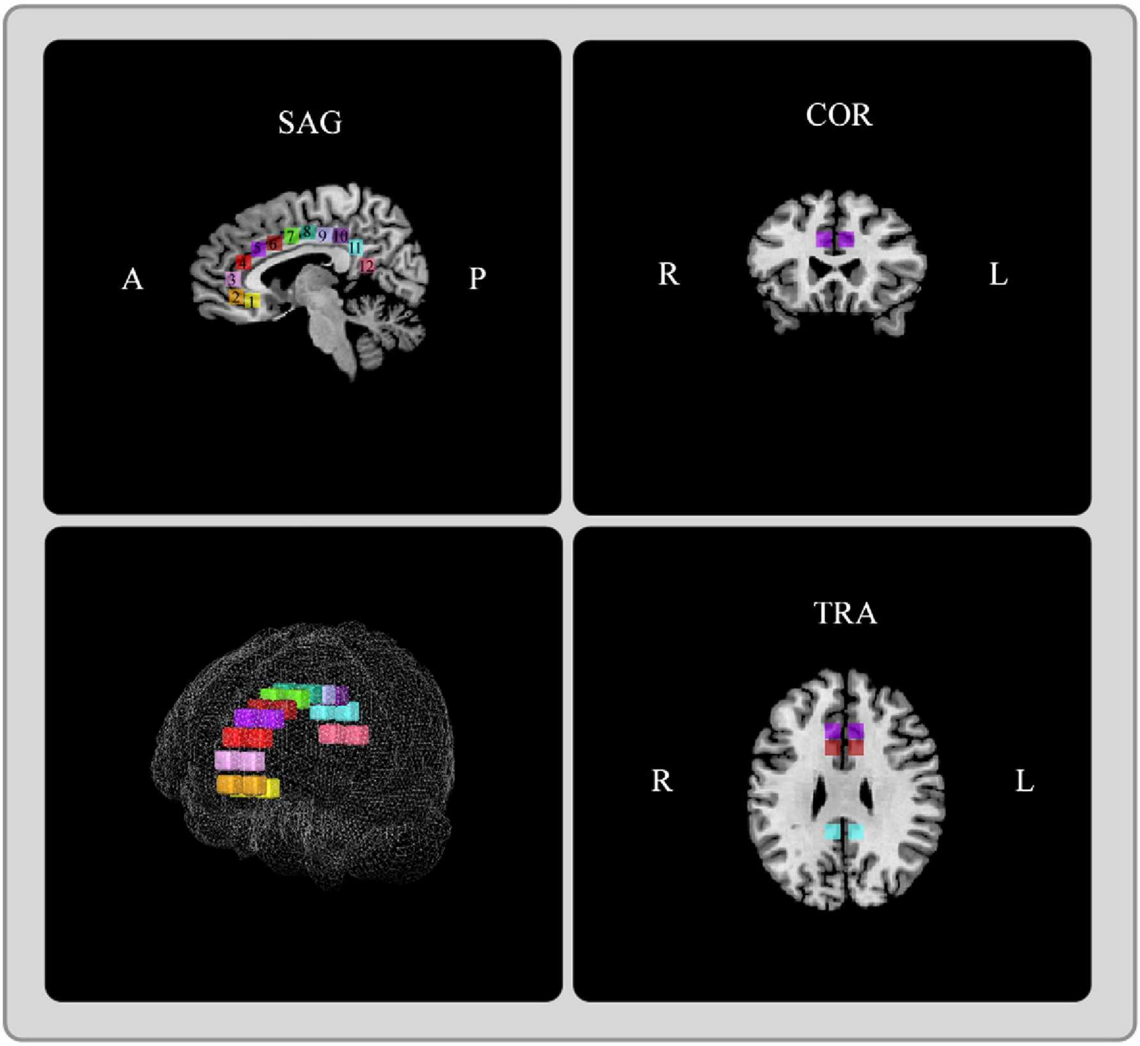

Fig. 1. In the *left upper panel*, the 12 bilateral ROIs are shown in a sagittal plan. ROIs were selected along the rostro–caudal axis of the cingulate cortex. In the *left panel* (*lower*), the twelve bilateral ROIs are tridimensionally shown. In the *right panel, upper and lower parts*, coronal and transversal sections are shown. The selection of the ROIs was not based on pre-existing subdivisions (anatomical, functional, histological) in order not to assume an *a priori* hypothesis; instead, our approach aimed at obtaining data-driven results. The choice of 12 consecutive bilateral ROIs of 10×10×10 mm along the rostral–caudal axis of the cingulate cortex was also motivated by the technical constraints of the MACM (see text for details).

computing statistical contrasts of pairs of ALE images (Laird et al., 2009a). Indeed these modifications were aimed to solve the several limitations known to exist in the original implementation: 1) the already mentioned fixed-rather than random-effect analysis, 2) the size of the modeled Gaussian that was specified by the user, and 3) the permutation *t*-test that was not anatomically constrained. Recent advances in the technique have modified the user-specified Gaussian model into an empirically determined quantitative estimate of the between-subject and between-template variability. This correction models the spatial uncertainty of each coordinate by weighting each study by the number of included subjects. These modifications have added statistical power to the method (Eickhoff et al., 2009) and have eliminated the possibility that ALE results may be driven by the results of a single study.

Table 1
Coordinates of the 12 ROIs.

ROI	X	Y	Z	Volume
1	7/−8	26	−6	10×10×10 mm
2	7/−8	37	−4	10×10×10 mm
3	7/−8	39	8	10×10×10 mm
4	7/−8	32	19	10×10×10 mm
5	7/−8	22	28	10×10×10 mm
6	7/−8	11	32	10×10×10 mm
7	7/−8	0	37	10×10×10 mm
8	7/−8	−11	39	10×10×10 mm
9	7/−8	−22	38	10×10×10 mm
10	7/−8	−33	37	10×10×10 mm
11	7/−8	−43	29	10×10×10 mm
12	7/−8	−51	17	10×10×10 mm

In our study, ALE maps were created by analyzing the pattern of coactivations of each of the 12 ROI. An ALE was performed for each ROI and associated coordinates separately. To attribute each of the ROIs to a functional network, we used a data-driven criterion of parcellation that grouped data in clusters according to their functional similarities (see next paragraph). ALE maps were computed at a False Discovery Rate (FDR)-corrected threshold of $p<0.05$ and visualized using Mricron (www.mricro.com) and BrainVoyager QX 2.0.

Network labeling and MACM-based parcellation

The labels for the MACM results shown in Fig. 3 were created as follows: 1) we first aimed to obtain a series of templates of the principal networks found to be present in the resting (Mantini et al., 2007) and active (Smith et al., 2009) brain. To do so, we applied an

Independent Component Analysis (ICA) decomposition on resting state datasets obtained from a group of seventeen participants who took part in a previous study (Cauda et al., 2010). This decomposition was done in accordance with Mantini and colleagues' procedure (Mantini et al., 2007) and produced six ICA-derived templates (default mode network, attentional, sensorimotor, anterior default mode network, uditive and visive); and 2) by performing a spatial correlation of these templates and each ROI-derived MACM map, we created a *spatial correlation profile* for each of the ROIs, in which the spatial correlation coefficients between each ROI and each of the six templates were stored. Only templates showing a significant ($p<0.05$) correlation with each ROI were included in the spatial correlation profile. These profiles were stored in the rows of Z, the *MACM profile matrix* of dimensions $Z \times Nv$, where Nv is the number of networks kept. To describe the degree of similarity between profiles, we computed the *functional similarity matrix* (S) that is the cross-correlation matrix of Z. To cluster the ROIs in groups, we used two different clustering algorithms: the K-means and the hierarchical clustering algorithms. The K-means algorithm is used to cluster *n* observations in *k* clusters in which each observation belongs to the cluster with the nearest mean. *K* initial means are randomly selected from the dataset and *k* clusters are created by associating every observation with the nearest mean. The centroid of each of the *K* clusters becomes the new mean. This procedure is then repeated until convergence is reached. In order to eliminate subjective biases, in the selection of the number of groups, we followed the methodology used by Johansen-Berg and colleagues (Johansen-Berg et al., 2004). Johansen-Berg and colleagues applied a spectral reordering algorithm onto a similarity matrix (obtained from probabilistic tractography data, but containing a similarity index as in our case) to find the reordering that minimizes the sum of element values multiplied by the squared distance of that element from the diagonal, hence forcing large values towards the diagonal. If the data contain clusters (representing seed ROI with similar connectivity), then these clusters will appear in the reordered matrix. Break points between clusters will represent locations where connectivity patterns change. Number of clusters were, on the basis of this reordered matrix, identified by visual inspection as groups of elements that were strongly correlated with each other and weakly correlated with the rest of the matrix.

To minimize the risk of inconsistent results obtained for the initial random placement of starting points, we computed the K-means clustering 256 times, as recommended by Nanetti and colleagues (Nanetti et al., 2009). The same clusters were identified 211 out of 256 times.

As we were interested in analyzing the hierarchical structure of the clusters of the cingulate cortex, we performed a hierarchical clustering to map a dendrogram of our ROI-wise clustering results. We used Cluster 3.0 (http://bonsai.ims.u-tokyo.ac.jp/~mdehoon/software/cluster/software.htm) for the calculation and TreeView (http://jtreeview.sourceforge.net/) to map dendrograms. The similarity matrix (S) was built using the Euclidean Distance and Centroid Linkage as clustering method. In Centroid Linkage Clustering, a vector is assigned to each pseudo-item, and this vector is used to compute the distances between this pseudo-item and all remaining items or pseudo-items using the same similarity metric that was employed to calculate the initial similarity matrix. The vector is the average of the vectors of all actual items contained within the pseudo-item. Thus, when a new branch of the tree is formed joining together a branch with n items and an actual item, the new pseudo-item is assigned a vector that is the average of the $n+1$ vectors it contains, and not the average of the two joined items.

Behavioral domain profiles and paradigm classes

Besides the functional connectivity of different portions of the cingulate cortex, we were interested in examining which mental processes are activated by each ROI. In BrainMap, metadata are organized under paradigm classes and behavioral domains. The 'paradigm class' is the experimental task isolated by the contrast. For a given experiment, multiple paradigm classes may apply. Paradigm classes include, among others, action observation, episodic recall, task switching etc. The 'behavioral domain' describes the categories and subcategories of mental operations likely to be isolated by the experimental contrast. Behavioral domains are classified in six main categories: cognition, action, perception, emotion, interoception or pharmacology. The behavioral domains and paradigm classes are established by the creators of the database. A complete list of BrainMap's behavioral domains can be accessed at http://brainmap.org/scribe/; description of the classification of behavioral domains and paradigm classes can be accessed at http://brainmap.org/scribe/index.html.

We first included in the analysis all behavioral domains and paradigm classes in which activations of each ROI were present. Afterwards, we calculated the percentage of occurrence of each behavioral domain and paradigm class with respect to the number of papers included in each ROI. Only behavioral domains and paradigm classes present in at least 5% of the papers selected for each ROI were submitted to the K-means clustering (see next paragraph).

Behavioral domain-based parcellation

The behavioral domain clustering was computed using the same methods as for the MACM-based clustering: ROI-related behavioral domain-based profiles were clustered by the K-means algorithm and the optimal number of clusters was calculated using the same method as for MACM-based network clustering. Similarly, ROI-related behavioral domain-based profiles were submitted to a hierarchical clustering using the Euclidean Distance and Centroid Linkage as clustering method.

Behavioral domain-based metaanalysis

To inspect if anatomically similar regions of the cingulate region show different patterns of co-activation, we performed a separate meta-analysis on the behavioral domains that were present in at least 5% of the total number of papers selected for each ROI: 'emotion', 'attention', 'pain', 'action execution', 'memory' and 'language'. For each domain we performed a separate meta-analysis using the BrainMap database (Laird et al., 2005). For the emotional domain the search limits were [Diagnosis = Normals] AND [Behavioral Domain = Emotion]. For the attentional domain the search limits were [Diagnosis = Normals] AND [Behavioral Domain = Cognition · Attention]. For the pain domain the search limits were [Diagnosis = Normals] AND [Behavioral Domain = Perception · Somesthesis · Pain]. For the action execution domain the search limits were [Diagnosis = Normals] AND [Behavioral Domain = Action · Execution]. For the memory domain the search limits were [Diagnosis = Normals] AND [Behavioral Domain = Cognition · Memory]. For the language domain the search limits were [Diagnosis = Normals] AND [Behavioral Domain = Cognition · Language].

Spatial probability maps

Spatial consistency of functional connectivity patterns across different domain-related ALE results was evaluated by computing probabilistic maps. At each spatial location, such maps represent the relative number of ALE values leading to significant results. The probability map is calculated by summing voxel value of each domain-related ALE result and dividing this value by the number of domains. ALE maps, before the probability maps creation, were thresholded at a False Discovery Rate (FDR)-corrected threshold of $p<0.05$ and visualized using Mricron (www.mricro.com) and BrainVoyager QX 2.0.

Results

Activation likelihood estimation (ALE) meta-analysis: maps of coactivations (MACM)

A total of 1131 studies were included in our meta-analysis corresponding to 1375 experiments, leading to a total of 18,976 foci. See Tabs S1–S12 of the supporting online materials for further details and for the number of studies included in each ROI.

Fig. 2 shows the ALE profiles of each ROI.

ROI 1 was found to be functionally connected with the amygdala, the orbitofrontal cortex, the ventromedial prefrontal cortex, the posterior insular cortex, the nucleus accumbens and the precuneus. ROI 2 shared important connectivity similarities with ROI 1, but it also showed stronger functional connectivity with the posterior cingulate cortex and weaker with the posterior insular cortex. ROI 3 besides some co-activations in common with ROI 2, showed functional connections with the anterior insular cortex, the striatum and the nucleus caudatus. ROI 4 showed co-activations with fronto-parietal areas. The activation profile associated with ROI 4 was characterized by an increase in the co-activation of ROI 4 and the dorsal anterior cingulate cortex and the absence of the co-activation with the amygdala. ROI 5 was found to be part of a network of co-activations encompassing the anterior insular cortex, the thalamus and the midbrain. No major functional differences were observed between ROI 6 and ROI 5. ROI 7 showed co-activations with the parietal cortex, the intra parietal sulcus and the middle frontal gyrus. ROI 8 was functionally connected with sensory-motor areas. Similarly, ROI 9 showed connections with motor cortices, but in addition, it showed increased co-activations with the supplementary motor area and visual areas. ROI 10 was active together with motor and visual areas, but limbic components re-appeared together with strong functional connections with the medial prefrontal cortex and the temporal parietal junction. ROI 11 was found to be part of a mesial fronto-parietal network (posterior part of the DMN see Raichle and Snyder, 2007) and showed further coactivations with some attentional-related areas such as the dorsolateral prefrontal cortex (DLPFC) and the anterior insula. Co-activations of ROI 12 were super-imposable to those of mesial fronto-parietal network of the DMN (Raichle and Snyder, 2007).

Fig. 3 shows that according to the MACM-based parcellation, the cingulate cortex can be divided in three clusters: ROIs 1, 2, 3, 11 and 12 were assigned to the first cluster, ROIs 4, 5, 6 and 7 to the second, ROIs 8, 9 and 10 to the third. Spatial distance between clusters in the

Fig. 2. Maps of co-activations of each ROI.

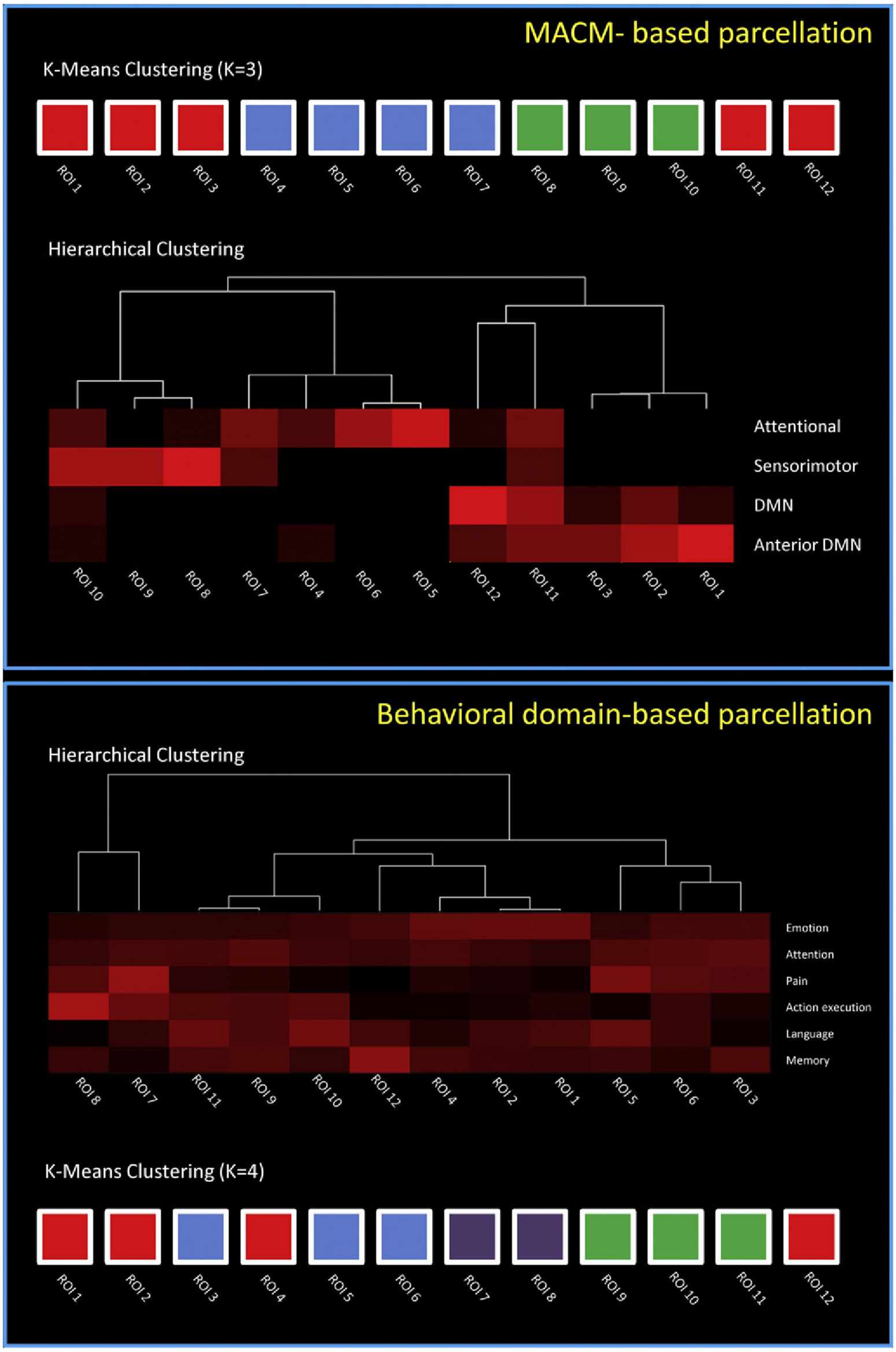

Fig. 3. In the *upper panel* the parcellation based on the MACM. Network labeling was done by correlating each ROI-derived MACM map to a template of the principal networks identified in the resting and active brain: default mode network (DMN), attentional, sensorimotor, anterior default mode network (anterior-DMN), uditive, visive. In this way we produced a spatial correlation map for each of the ROI and each of the template (see text for details). Only significant correlations were kept (default mode network, attentional, sensorimotor, anterior default mode network). The K-means clustering produced three subdivision of the cingulate cortex. The K-means algorithm is used to cluster *n* observations in *k* clusters in which each observation belongs to the cluster with the nearest mean. *K* initial means are randomly selected from the dataset and *k* clusters are created by associating every observation with the nearest mean. In the dendrogram, near elements are more similar. The shades of red represent how much each ROI can be considered as associated to a MACM profile. Brighter reds mean a greater association. In the *lower panel* the parcellation based on the behavioral profiles. Network labeling was done in accordance with the BrainMap database. The K-means clustering was used to cluster the observations. Again, as in the MACM the distance between clusters represents their similarity (the closer, the more similar). The shades of red represent how much each ROI can be considered as associated to a behavioral profile. Please see text for further details.

dendrogram represents their degree of similarity: the closer they are, the more their functional similarity. In cluster 1, ROIs 2 and 3 were identified as more functionally similar to each other than to ROI 1. Within the same cluster, ROIs 11 and 12 formed another sub-cluster. In cluster 2, ROIs 5 and 6 were more similar to each other than to ROIs 4 and 7. In cluster 3, ROIs 8 and 9 were more similar to each other than

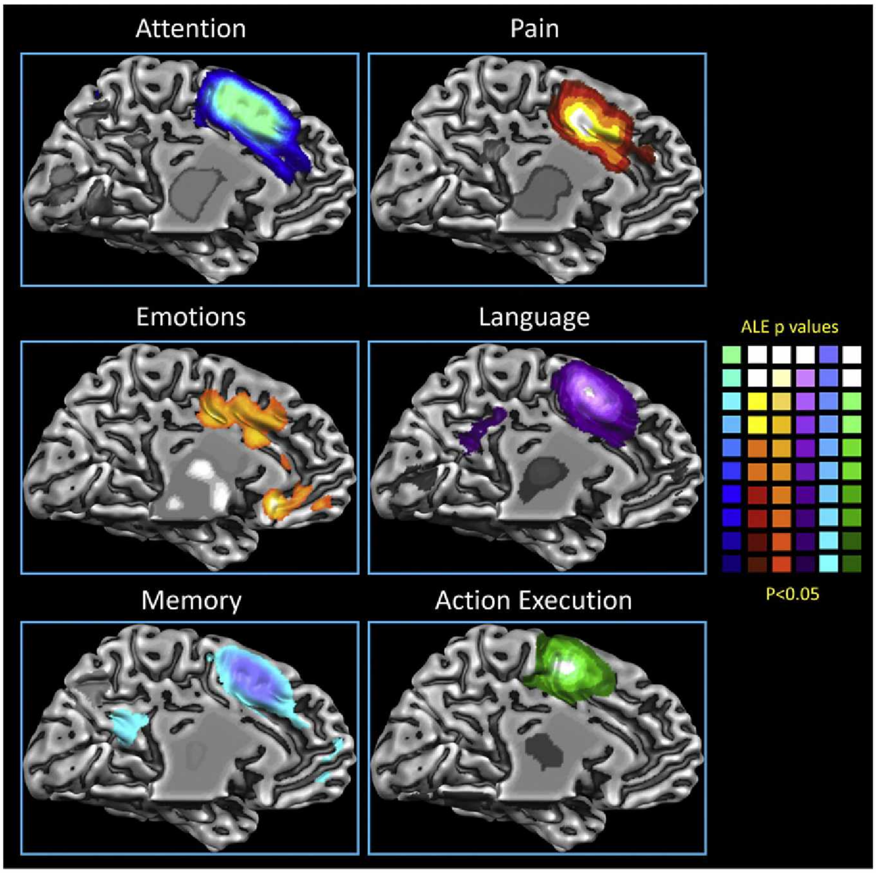

Fig. 4. ALE maps of behavioral profiles.

to ROI 10. Additionally, cluster 2 and 3 were more similar to each other than to cluster 1.

Behavioral domain profiles

Six behavioral domains were present in at least the 5% of the papers selected for each ROI (see methods section). They were labeled as follows: 'emotion', 'attention', 'pain', 'action execution', 'memory' and 'language'. In this case, labeling was chosen in accordance with the labeling of the BrainMap database. We then identified the paradigms that more often activated each ROI, using the same criterion as for the behavioral domains.

Activity in ROI 1 and 2 was mainly correlated with reward-related tasks, pertaining to the emotional behavioral domain. ROI 3 was found to be particularly active for tasks related to the behavioral domain of attention. At the same time, it was associated with pain discriminative paradigms. ROI 4 showed a superimposition of activity related to emotional and attentive tasks and was related to reward and pain discriminative paradigms. ROI 5 was activated by various behavioral functions, such as attention, language and perceptive somatic pain, but it was particularly active in pain discrimination paradigms. ROI 6 showed a pattern similar to that of ROI 3. ROI 7 was specifically active for pain discrimination paradigms, despite being also part of the network underpinning other behavioral functions such as action execution and attention. ROI 8 showed a motor pattern, thus being active in action execution tasks and finger tapping paradigms. ROI 9 was more associated with memory and attentional tasks and activated by paradigms of film viewing and visual pursuit. ROI 10 showed a more 'linguistic' pattern of activation, being associated to linguistic functions, semantic discrimination and episodic recall paradigms. ROI 11 was found to be involved in several behavioral functions and active for reward and language paradigms. Finally, ROI 12 was more associated to memory abilities and reward and was active in n-back and face discrimination tasks.

Fig. 3 shows how the subdivision of the cingulate cortex according to the behavioral domain yielded four clusters: cluster 1 was constituted by ROIs 1, 2, 4 and 12, cluster 2 by ROIs 3,5 and 6, cluster 3 by ROIs 7 and 8 and cluster 4 by ROIs 9, 10 and 11. Although pertaining to the same cluster, ROIs 1 and 2 were more similar to each other than ROI 4 and ROI 12 formed a separate sub-cluster. In cluster 2, ROIs 3 and 6 were more similar to each other than ROI 5. In cluster 4, ROIs 9 and 11 were more similar to each other than ROI 10. As a whole, clusters 1 and 4 were more similar to each other whereas cluster 3 remained a separate cluster.

Fig. 3 also depicts the functional complexity of some of the ROIs. Some portions of the cingulate cortex were in fact highly correlated to specific behavioral domains (e.g. ROIs 1 and 2, please refer to the legend of Fig. 3 for more details), whereas others activated for a plurality of tasks and were correlated to different behavioral domains.

Behavioral domains meta-analysis

To further investigate the involvement of some portions of the cingulate cortex in a plurality of tasks, we performed a separate meta-analysis for the six domains that were more frequently found present in the cingulate cortex (and identified as previously explained): attention, pain, language, action execution, emotions and memory (see Tabs S13–S18 of the supplementary on line material and Fig. 4).

The results of the separate meta-analysis for the six domains that were more frequently found present in the cingulate cortex led to the identification of 314 papers using a total of 5253 subjects in 2188 experiments identifying 17806 locations for the attentional domain; of 78 papers using a total of 989 subjects in 250 experiments leading to 2276 locations for the pain domain; of 455 papers using a total of

7036 subjects in 1945 experiments leading to 16222 locations for the language domain, of 94 papers using a total of 1491 subjects in 117 experiments leading to 1772 locations for the action execution domain; of 314 papers using a total of 5282 subjects in 1272 experiments leading to 8526 locations for the emotion domain; of 388 papers using a total of 7903 subjects in 1455 experiments leading to 12057 locations for the memory domain.

To investigate if the same areas of the cingulate cortex were recruited in various behavioral domains, we calculated a probabilistic map considering the percentage of superimposition of the ALE-generated maps and the results of the behavioral-domain based meta-analysis. The results of this analysis showed that ROI 6 and 7 were virtually active for all the six behavioral domains (see Fig. 8). More specifically, the probabilistic map represented in Fig. 8 shows that in the region covered by ROI 7 and in minor portion in ROI 6 there is a 100% superposition of all six behavioral domains.

Discussion

The aim of the present study was to picture the functional complexity of the cingulate cortex by pooling together activations extracted from over 1000 studies in the BrainMap database. The results indicate that the activations of the cingulate cortex can be broadly reduced to three functional clusters and four behavioral domains (see Fig. 3). However, they also underline the complexity of some portions of the cingulate area, which were found to activate for a plurality of behavioral domains.

The discussion will follow three main lines: we will first discuss the co-activation profiles of the ROIs and the functional clusters, then we will analyze the behavioral domains (ROI per ROI and as a cluster) and finally we will discuss the involvement of some portions of the cingulate cortex in a plurality of tasks.

ALE profiles of each ROI and functional clusters

ROIs 1 and 2 were found to have important coactivations with the amygdala, the orbitofrontal cortex, the ventromedial prefrontal cortex, retrosplenial cortices and the nucleus accumbens (see also Beckmann et al., 2009; Cauda et al., in press-a; Yu et al., 2011). The functional similarity found between ROIs 2 and 3 may indeed reside in their being “transition regions” wherein cognitive and affective processes are integrated (Devinsky et al., 1995; Margulies et al., 2007). ROI 3 was found to be coactive with the insular cortex. The joint activation of the anterior insular cortex and the anterior cingulate cortex is frequently reported (Craig, 2009; Medford and Critchley, 2010). This supports the idea that these two regions serve as complementary limbic sensory and motor regions working together (Craig, 2009), involved in the production of interoception and subjective feelings, coordinating appropriate responses to internal and external events. In particular, the anterior insular cortex is thought to be involved in the re-representation of interoceptive information thus participating in bodily awareness (Craig, 2009).

ROIs 4 and 5 were found to be part of the fronto-parietal networks that have been proposed to act together for the selection of where and to what allocate attention: the dorsal and ventral fronto-parietal networks (see Corbetta et al., 1991; Corbetta et al., 2008; Menon and Uddin, 2010; Seeley et al., 2007). Furthermore, ROIs 5–7 showed conjunct activity with subcortical regions such as the thalamus and the midbrain and were also part of a network including the anterior insular cortex and the medial thalamus. All these areas are some of the main constituent of the so-called ‘Core System’ (Dosenbach et al., 2006; Medford and Critchley, 2010; Nelson et al., 2010) which is involved in the implementation of task-sets and sustained ‘set-maintenance’ over entire task epochs.

Functional links between the ventral attentional network and the norephinephrine activity of the locus coeruleus have been outlined by neurocomputational models (Aston-Jones, 2005; Bouret and Sara, 2005; Dayan and Yu, 2006) and it has been shown that subcortical regions like the superior colliculus are involved in stimulus-driven and goal-driven mechanisms of attention (Bell et al., 2004; Fecteau et al., 2004; Rafal et al., 1988; Sapir et al., 1999; Tamietto et al., 2010). Moreover, the pulvinar nucleus is involved in the modulation of the physical saliency of a stimulus in both humans and non-humans primates (Snow et al., 2009; Tamietto and de Gelder, 2010) and recruited for covert forms of goal-directed searches (Fairhall et al., 2009).

ROI 8 and 9 showed a more pronounced pattern of sensorimotor connectivity. Three areas located in such regions, often described as cingulate motor zone (Barbas, 2000; Mayka et al., 2006; Morecraft et al., 2007; Morecraft and Van Hoesen, 1998), have been shown to be involved in motor control. These areas are situated within the cingulate sulcus and consist in: (i) a rostral (CMAr) and (ii) ventral (CMAv) parts lying in the ventral bank of the cingulate sulcus. The third area, the dorsal cingulate motor area (CMAd) is located in the dorsal bank of the cingulate sulcus. Each of such cingulate motor areas is characterized by cytoarchitectonic differences (Cauda et al., in press-b; Picard and Strick, 1996).

The pattern of connectivity of ROI 10 comprised areas involved in memory recall and attentional networks (Binder et al., 2009). The area activated by the semantic system in this study was located some millimeters more rostrally to that found by other studies. This region has been linked to episodic and visuospatial memory functions (Aggleton and Pearce, 2001; Epstein and Higgins, 2007; Gainotti et al., 1998; Rudge and Warrington, 1991; Vincent et al., 2006), and has strong reciprocal connections with the hippocampal complex via the cingulum bundle (Kobayashi and Amaral, 2003, 2007; Morris et al., 1999). The mid/posterior cingulate cortex is affected early in the course of Alzheimer's disease (AD), in which the episodic memory encoding deficit is often a marker (Desgranges et al., 2002; Nestor et al., 2003). Posterior ROIs showed a mixed connectivity with DMN and the attentional salience detection system. These areas have been recently associated to gain-specific activation (increased activation for increased gain, but no change in activation in relation to loss) (Fujiwara et al., 2009). The role in the evaluation of gain is well expressed in the pattern of meta-analytic connectivity. Indeed, the salience detection system is strongly connected to the ventral striatum and shares several areas with the reward system.

As far as the relationship between co-activation and functional connectivity is concerned, it has been shown that MACM and resting state functional connectivity may lead to similar results (Cauda et al., in press-a). Indeed, it is difficult to explain how such coactivations of brain areas across different paradigms and studies may emerge in absence of any functional connectivity between these areas (as discussed in Koski and Paus, 2000; Laird et al., 2009a; Postuma and Dagher, 2006; Smith et al., 2009). The current opinion (Koski and Paus, 2000; Laird et al., 2009a; Postuma and Dagher, 2006; Smith et al., 2009) is to interpret the functional coactivations as a form of functional connectivity. Furthermore the mapping of functional connectivity via coordinate-based meta-analysis has been validated by comparing the results of MACM to resting-state connectivity (Smith et al., 2009). Both approaches produced very consistent results.

When using a clustering procedure, all different patterns of functional connectivity were grouped in three main clusters, that may be labeled as ‘self-referential’, ‘attentive’ and ‘sensory-motor’. The clustering pinpointed to a strict interconnection between anterior and posterior parts of the cingulate cortex, repeatedly found in resting state functional connectivity. The clustering also supported the existence of a large interconnected portion of the cingulate cortex devoted to self referential functions; an anterior dorsal section devoted to attentional functions and a posterior area characterized by sensory-motor functions and language. Palomero-Gallagher and

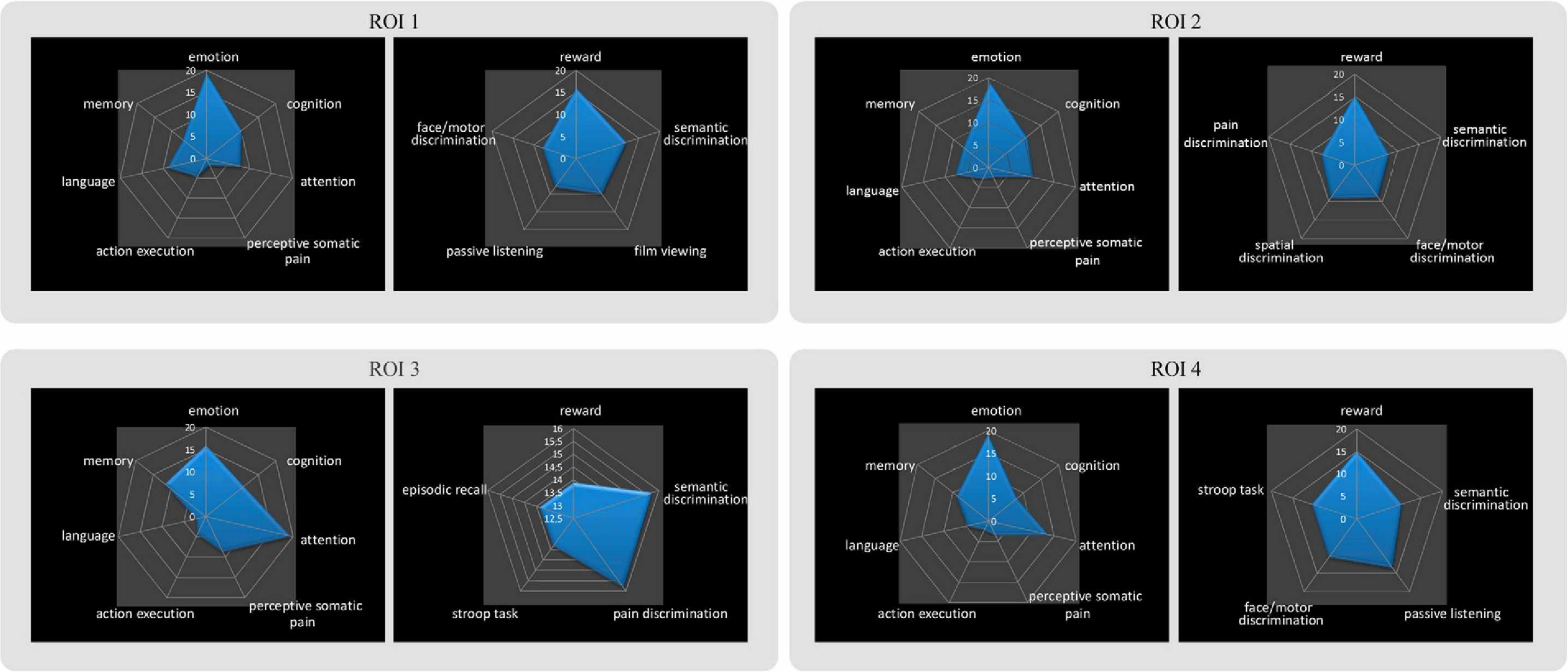

Fig. 5. Shows the behavioral domains and paradigm classes for each ROI. Here, ROIs 1–4 are presented. Behavioral domains are on the left-hand side, paradigm classes on the right-hand side. Please note that the domain 'cognition' was never considered in our analysis. Each vertex of the polygon represents a behavioral domain (left panel) or a paradigm class (right panel). The percentage of occurrence of each behavioral domain and paradigm class is shown on the radial axis of the polygon. Lower percentages of occurrence are closer to the center. Higher percentages of occurrence are closer to the vertexes.

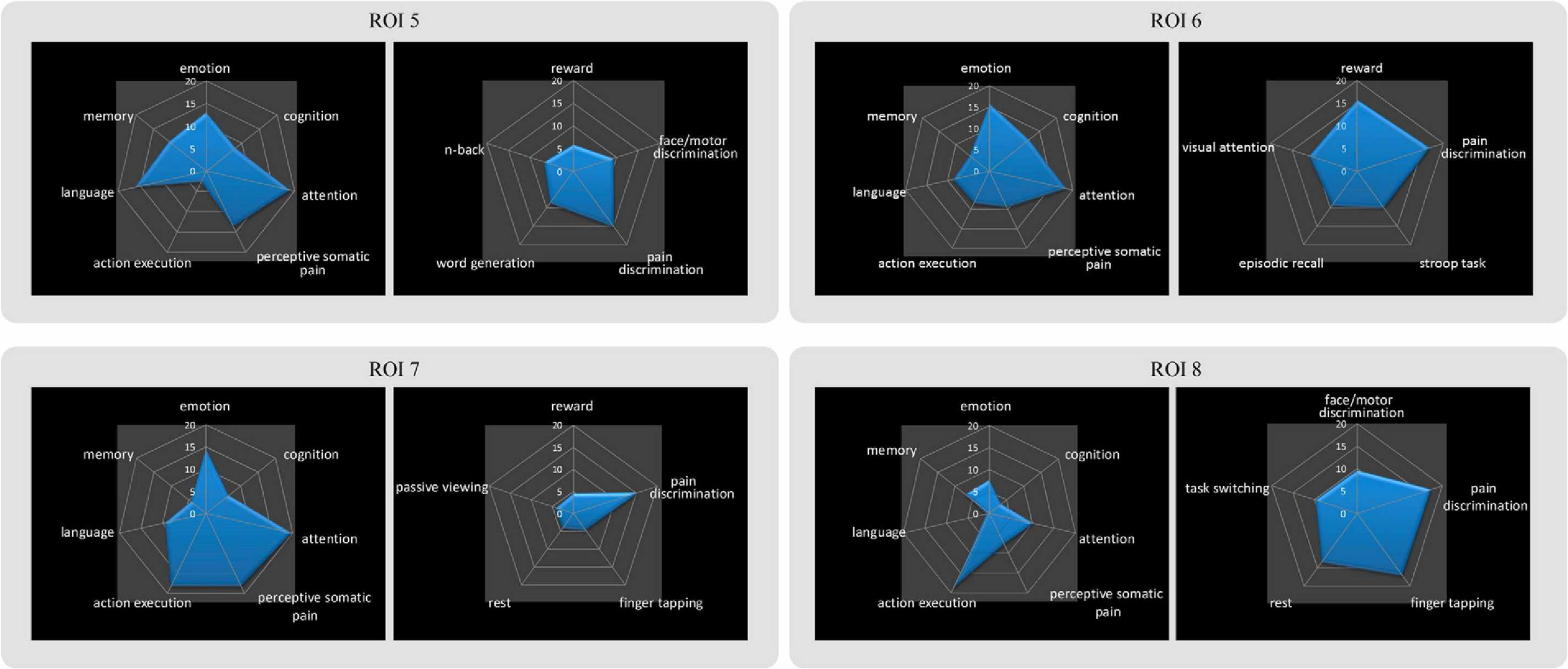

Fig. 6. Shows the behavioral domains and paradigm classes for each ROI. Here, ROIs 5–8 are presented. Behavioral domains are on the left-hand side, paradigm classes on the right-hand side. Please note that the domain 'cognition' was never considered in our analysis. Each vertex of the polygon represents a behavioral domain (left panel) or a paradigm class (right panel). The percentage of occurrence of each behavioral domain and paradigm class is shown on the radial axis of the polygon. Lower percentages of occurrence are closer to the center. Higher percentages of occurrence are closer to the vertexes.

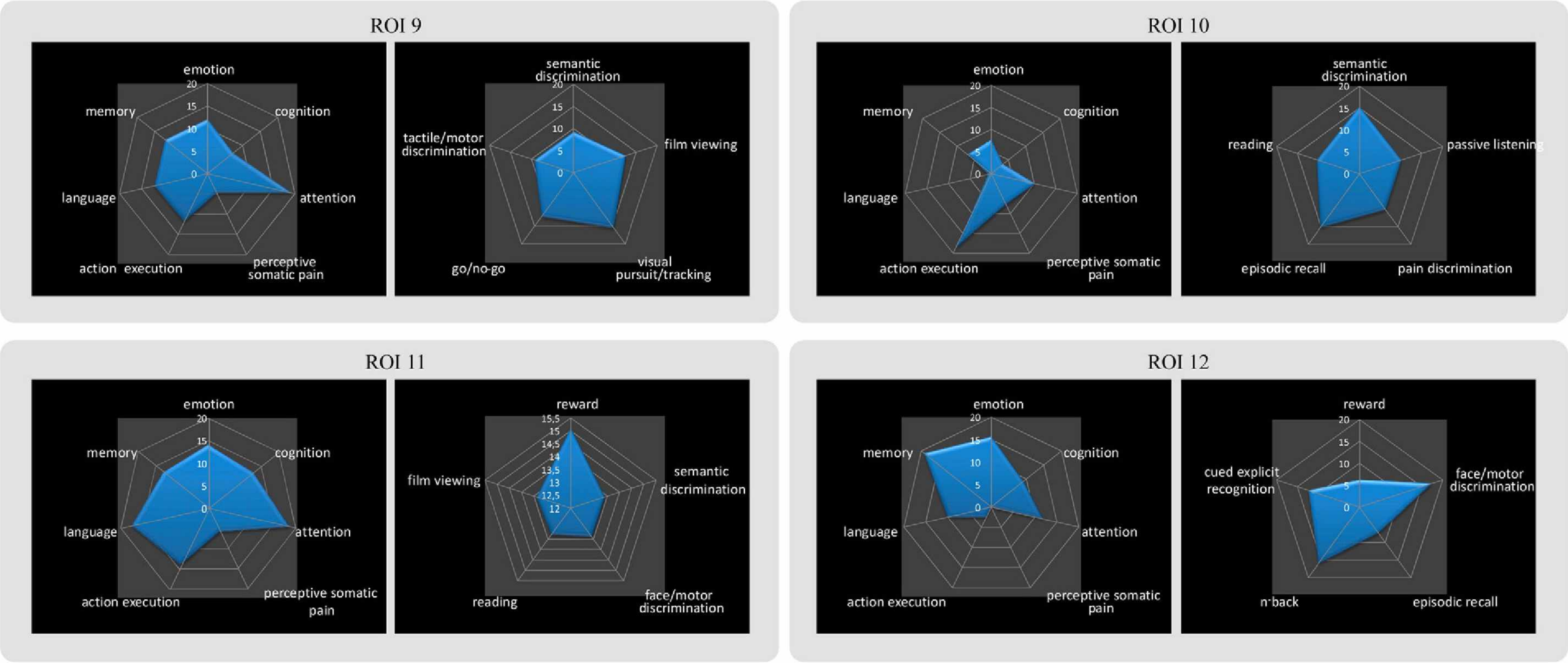

Fig. 7. Shows the behavioral domains and paradigm classes for each ROI. Here, ROIs 9–12 are presented. Behavioral domains are on the left-hand side, paradigm classes on the right-hand side. Please note that the domain 'cognition' was never considered in our analysis. Each vertex of the polygon represents a behavioral domain (left panel) or a paradigm class (right panel). The percentage of occurrence of each behavioral domain and paradigm class is shown on the radial axis of the polygon. Lower percentages of occurrence are closer to the center. Higher percentages of occurrence are closer to the vertexes.

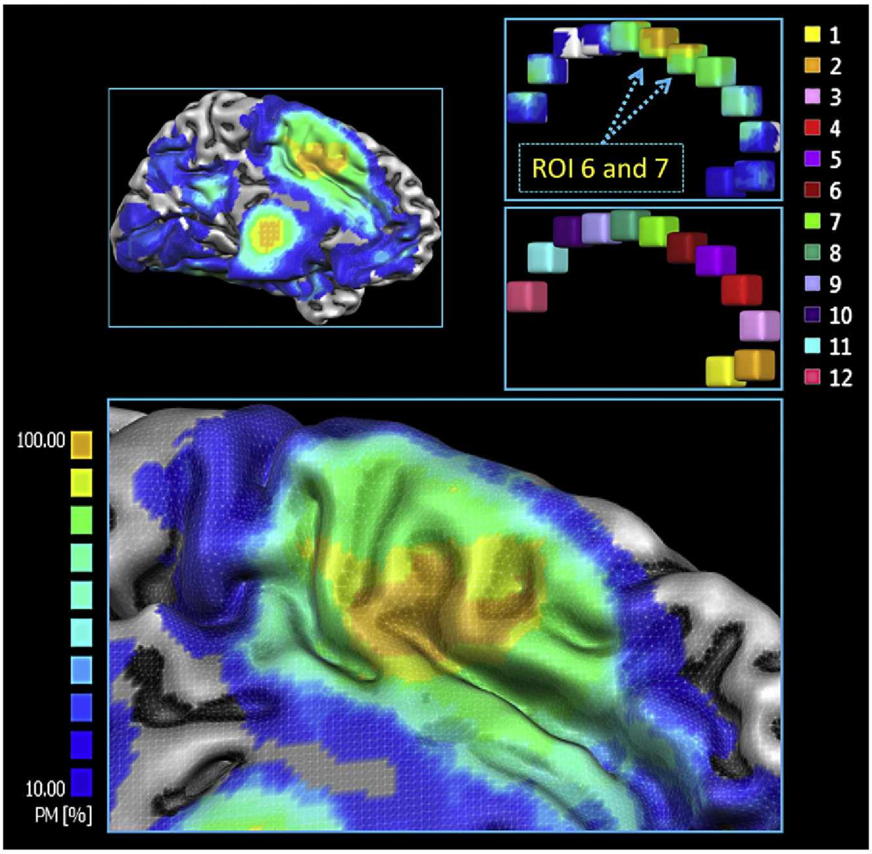

Fig. 8. Shows the spatial probability maps of each ROI. At each spatial location, such maps represent the relative number of ALE values leading to significant results. The probability map is calculated by summing voxel value of each domain-related ALE result and dividing this value by the number of domains. In ROIs 6 and 7 there is a virtual overlap of all behavioral domains.

colleagues (Palomero-Gallagher et al., 2009) by using a hierarchical clustering found support for the four, instead of three, subregions models. Our MACM data are more in favor of a division in three functional clusters. However, these results are only in apparent contrast with Palomero-Gallagher's ones. Indeed, it has to be noted that their clustering was based on the postmortem analysis of receptor binding according to the degree of similarity of each area's receptor architecture. In contrast, we propose a three-region subdivision of the cingulate cortex based on functional connectivity evidences.

Behavioral profiles and behavioral clusters

Activations in ROI 1 and 2 were highly correlated to the behavioral domain of emotion and to reward-related tasks. Anterior portions of the cingulate cortex have been reported repeatedly as central to reward-related tasks (Haber and Knutson, 2010). Indeed, recordings from neurons in the anterior cingulate cortex (which receive important dopaminergic projections, Williams and Goldman-Rakic, 1998) demonstrated that such neurons encode reward prediction combining information about reward magnitude and reward probability (Amiez et al., 2006; Matsumoto et al., 2003; Rushworth and Behrens, 2008). Similarly, another area of the frontal lobes, the orbitofrontal cortex, is involved in elaboration of reward and in decision making, in particular of the expected value of a reward (Sul et al., 2010). Lesion studies however suggest that the two areas code different aspects of reward and reward-related behaviors. In humans and animals, lesions to the orbitofrontal cortex lead to the preference of small immediate rewards over larger and delayed ones (Kheramin et al., 2002), but do not impair the ability of evaluating the effort that has to be made to obtain a reward. Conversely, lesions to the anterior cingulate cortex do not alter delay-based decision tasks, but impair the ability in effort based decision-making tasks (Rudebeck et al., 2006; Walton et al., 2003; Walton et al., 2002).

Subgenual anterior cingulate cortex is thought to be implicated in the regulation of mood. It has been demonstrated that patients suffering from major depressive disorders (MDD) and bipolar disorders have a reduction in the mean gray matter volume of this areas irrespective of the mood state (Drevets et al., 1997; Ongur et al., 1998). ROIs 3 and 4 may indeed reflect the area of the cingulate cortex where the distinction affective/cognitive starts to take place (Devinsky et al., 1995). It has been suggested that rather than looking for a specific role of the subregion of the cingulate cortex implicated, it would be more useful to conceive that both kinds of stimuli may share similarities (e.g. they cause an avoidance reaction) and that it is this avoidance reaction which generates the response of the cingulate cortex, and not emotional or painful stimuli *per se* (Vogt, 2005). For instance, the activation of ROIs 4 in tasks of pain discrimination, reward and attention may reflect the property of such areas, working as saliency detector and saliency map (Cauda et al., 2011; Corbetta et al., 2008; Corbetta and Shulman, 2002).

ROI 3, 5 and 6 were predominantly associated with the behavioral domains of attention and activated by pain related paradigms. The interplay between attention and pain is a complex and hot area of research (Seminowicz and Davis, 2007a, b; Wiech et al., 2008). Attention and its counterpart distraction have been found to modulate both the perception of pain and the brain responses associated to it (Bantick et al., 2002; Peyron et al., 2000; Rainville et al., 1997) but the characteristics of the painful stimulus of readily grasping attention, seriously limit the possibility of studying the interaction between attention and pain as it is done in other sensory domains (e.g. grading the capability of a painful stimulus of grasping attention, for a review on the caveats and possible confounding aspects see (Seminowicz and Davis, 2007b; Wiech et al., 2008)). It has also been suggested that a great part of the response of the cingulate cortex to pain mainly reflects the activity of a multimodal saliency detector system (Downar et al., 2000; Iannetti and Mouraux, 2010; Legrain et al., 2011; Mouraux et al., 2011; Valentini et al., in press).

In support of the multimodal and multifunctional profile of the cingulate cortex, ROI 6 and 7 were found to be virtually active for all the behavioral domains. (see next paragraph).

Also, from Fig. 3 it can be noted that ROI 8 as well was involved in a variety of behavioral domains. Anatomically, this portion of the cingulate cortex has been identified as the cingulate motor zone. The cingulate motor zone is prevalently involved in action execution and motor paradigms. Interestingly, this area is also involved in pain discrimination paradigms as confirmed by several fMRI and LEP studies (Bentley et al., 2003; Bentley et al., 2001; Bentley et al., 2002).

Moving caudally (ROI 8 to 9), an increase in the involvement in semantic as well as attentive paradigms is observable. The mid/posterior cingulate cortex has been found to be mainly involved in semantic and language tasks. This observation is supported by findings (see Binder et al., 2009) which found the activation, among other areas, of the posterior cingulate cortex for the semantic system (i.e. the knowledge about people, concepts, objects, self, etc.). Additionally, activation of posterior portions of the cingulate cortex has been repeatedly found in relation to mnemonic and emotional tasks. Our results confirm previous findings of functional connectivity studies in humans (Cauda et al., 2010) and tracing experiments in primates (Parvizi et al., 2006) that showed selective interconnectivity between the posterior cingulate cortex and the parahippocampal formation in subserving episodic memory retrieval. Posterior parts of the cingulate cortex have been recently associated to gain-specific activations (Fujiwara et al., 2009). Several fMRI studies (Daselaar et al., 2004a; Daselaar et al., 2004b; Kao et al., 2005; Miller et al., 2008; Otten and Rugg, 2001; Shrager et al., 2008; Wagner and Davachi, 2001) have shown deactivation in the posteromedial cortex extending into the posterior cingulate cortex during memory encoding. These deactivations have been interpreted as the result of the reallocation of neuronal resources needed for efficient cognitive processing. The posteromedial cortices have been shown to be involved in self-referential and reflective activity (Addis et al., 2004; Burianova et al., 2010; Cauda et al., 2010; Greicius et al., 2003; Gusnard et al., 2001; Johnson et al., 2009; Johnson et al., 2006; Svoboda et al., 2006). Moreover, several studies have found a greater activation in the posteromedial cortices in proportion to the strength or certainty of the memory decision, indicating that this region seems to be specifically involved in memory retrieval (Chua et al., 2006; Svoboda et al., 2006; Wagner et al., 2005; Wheeler and Buckner, 2004). Indeed patients with focal lesions in this region suffer from amnestic syndromes (Gainotti et al., 1998; Heilman et al., 1990; Katai et al., 1992; Rudge and Warrington, 1991; Takayama et al., 1991; Valenstein et al., 1987). The posterior cingulate cortex has been described as involved in the processing of valence and arousal of affective pictures (Nielen et al., 2009). Activation of this area in emotional tasks may reflect episodic memory involvement during evaluation of positively valence arousal.

Furthermore, these areas also showed an involvement in saliency detection which have been related to the 'wanting' component of reward (Berridge et al., 2009). Several human functional magnetic resonance imaging (fMRI) studies have confirmed this finding showing an increased posterior cingulate activation in relation to reward (Ernst et al., 2004; Izuma et al., 2008; Marsh et al., 2007; Nieuwenhuis et al., 2005; O'Doherty et al., 2001).

The parcellation of the cingulate cortex based on ALE maps (MACM) provided three functional clusters, whereas the parcellation based on the behavioral profiles provided four clusters and a more precise profile (see Fig. 3 in which the color of the square represents the degree of functional similarity). The clustering based on the behavioral domains (see Figs. 3 and 5–7) divided the cingulate region in four portions, whose profile is very similar to that of the previous MACM-based parcellation. However, the behavioral domain-based parcellation yields to an additional cluster in the midcingulate cortex. This difference would suggest that a parcellation of the cingulate cortex based on behavioral profiles can give a more fine-grained picture of the functionality of this area.

Behavioral based metanalysis and spatial probability maps

To inspect if anatomically similar regions of the cingulate region showed different patterns of co-activation, we first performed a separate meta-analysis for the six domains that were more present in the cingulate cortex; then we calculated a probabilistic map considering the percentage of superimposition of the ALE-generated maps and the results of the behavioral-domain based meta-analysis. Indeed, in ROIs 6 and 7 there was a virtual overlap of all 6 behavioral domains. This supports the possibility that similar portions of the cingulate cortex may indeed activate for different behavioral domains. This interesting finding can be explained by various possibilities: 1) some portions of the cingulate cortex may act as "hub" areas interconnecting different networks. Recently He and colleagues (He et al., 2009) suggested that the whole brain works in a modular fashion, but specific modules communicate through "hub" areas. These hub areas would be higher order associative areas able to link different smaller networks. This possibility supports the suggestion proposed by Vogt and colleagues (Vogt, 2005) for which it may be a more useful approach to consider that such portions of the cingulate area, rather than being primarily involved in specific tasks, may be involved in activities common to several tasks; 2) alternatively, these results may be explained by limitations in the current methodology and future more fine grained results may provide more precise glimpses over the functionality of portions involved in several tasks.

Conclusions

The cingulate cortex is a fascinating and complex region functionally involved in a broad variety of tasks and richly interconnected with the rest of the brain. Its structural and functional divisions are being progressively unveiled. However, to our knowledge, this is the first study which has systematically investigated the activations of the cingulate cortex including over 1000 published neuroimaging studies. Our results show the existence of a more specific functional characterization of some portions of the cingulate cortex, but also a great multifunctionality of others. It remains an open question as whether this is a peculiarity of this "hub" area or the result of the limits of the methodology used.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.03.066.

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