Classification: Biological Sciences; Neuroscience

Title: Functional specialization and complexity of human medial frontal cortex

Alejandro de la Vega[12], Luke J. Chang3, Marie T. Banich[12], Tor D. Wager[12] and Tal Yarkoni[4]

[1] Department of Psychology and Neuroscience, University of Colorado Boulder, Muenzinger D244, 345 UCB, Boulder, CO 80309-0345 [2] Institute of Cognitive Science, University of Colorado Boulder, 345 UCB, Boulder, CO 80309-0345 [3] Department of Psychological and Brain Sciences, Dartmouth College, 6207 Moore Hall. Hanover, NH 03755 [4] Department of Psychology, University of Texas at Austin, SEA 4.20, 108 E. Dean Keeton Stop A8000, Austin, TX 78712-1043

Corresponding Author: Alejandro de la Vega, Department of Psychology and Neuroscience, University of Colorado Boulder, Muenzinger D244, 345 UCB, Boulder, CO 80309-0345, 650-315-9536, delavega@colorado.edu

Keywords: medial frontal cortex, neuroimaging, cognitive control, affect

Abstract

The human medial frontal cortex (MFC) has been the subject of intense study, having been associated with many psychological processes, including motor processing, goal-directed behavior and affect. However, there is a scarcity of comprehensive efforts to map these wide-ranging processes to MFC anatomy. We systematically created a functional-anatomical mapping of MFC from a diverse database of nearly 10,000 neuroimaging studies. Using a data-driven approach, we identified putatively separable regions of MFC at various spatial scales on the basis of co-activation patterns with the rest of the brain, revealing three broad functional zones along a rostro-caudal axis composed of 2-4 smaller sub-regions each. The three functional zones co-activated with different brain-wide networks while the subregions within each zone showed subtle shifts in co-activation within those networks. We then used multivariate classification to identify which psychological concepts best predicted activity in each region, revealing similarly distinct patterns of functional specialization across the three broad functional zones. However, we also identified subtle shifts in functional specialization within each zone, which suggest existing accounts of convergence in MFC may be overstated.

Significance Statement

Alejandro De La V..., 9/21/2015 10:44 PM

Comment [1]: Authors must submit a 120-word-maximum statement about the significance of their research paper written at a level understandable to an undergraduate-educated scientist outside their field of specialty. The primary goal of the Significance Statement is to explain the relevance of the work in broad context to a broad readership. The Significance Statement appears in the paper itself and is required for all research papers.

The medial frontal cortex is a cortical area that has been associated with many psychological processes using functional MRI. The ubiquity of this areas activation, however, makes it challenging to understand how these processes are anatomically organized. We conducted a meta-analysis across nearly 10,000 studies to comprehensively map psychological function to discrete brain regions in medial frontal cortex. We discovered three distinct zones that differed substantially in function and were composed of nine smaller subregions that showed smaller

functional changes. This study provides a comprehensive functional map of the human medial frontal cortex using relatively unbiased data-driven methods.

Introduction

The medial frontal cortex (MFC) is a broad area of the brain encompassing many functionally distinct foci that have been associated with a wide variety of cognitive states using functional neuroimaging. For example, the supplementary motor area (SMA) and pre-SMA, have been associated with the planning and initiation of movements (1-3), while nearby dorsal anterior cingulate cortex (ACC) has been implicated in various aspects of cognitive control, such as conflict (4-6) and error processing (7, 8), and is thought to be important region for pain processing (9-11). Further anterior, medial prefrontal cortex (mPFC) and subgenual ACC have been shown to be important for a variety of affective processes, including emotion (12, 13), autonomic function (14), and valuation (15, 16). Furthermore, portions of mPFC have also been associated with a variety of stimulus-independent internally oriented processes, such as mentalizing (17, 18) and autobiographical memory (19).

Despite the enormous amount of neuroimaging research on focal regions of MFC, there have been few large-scale efforts to comprehensively map function to medial frontal anatomy across the full range of cognitive and affective states. Since most researchers are intimately familiar with one particular domain of cognition, most meta-analyses are necessarily restricted to a small subset of empirical findings relevant to the cognitive states or region under investigation. Even those meta-analyses that attempt to take a inter-disciplinary look at MFC typically only include a subset of cognitive states hypothesized to be important (e.g. (12, 20) or restrict themselves to a small region of interest (e.g. (21). The constrained scope of such meta-analyses is further hampered by the limited ability to draw conclusions about the relative specificity of brain activity to particular cognitive processes— a limitation widely known as the reverse

inference problem (22). This concern is particularly acute in the case of MFC regions pre-SMA and dACC, suggesting low selectivity to a given domain (23, 24).

Here we attempt systematically create a comprehensive functional-anatomical mapping of MFC using Neurosynth, a diverse large-scale functional neuroimaging database of over 10,000 studies (24). We first clustered MFC voxels into functionally homogeneous clusters at different spatial scales based on their meta-analytic co-activation with the rest of the brain (25-27), revealing three distinct zones along the rostro-caudal axis which further fractionated into nine sub-regions. We characterized the cognitive profiles of these clusters using multivariate classification analyses and found that the three functional zones accounted for a large portion of functional variation; however, we also found fine-grained variation in functional specialization between sub-regions within a functional zone. Collectively, our results reveal considerable diversity in the functional roles of discrete MFC subregions, provide insight into the spatial topography of MFC at several different scales, and suggest that previous studies may have overstated the case for the convergence of different processes in MFC.

Results

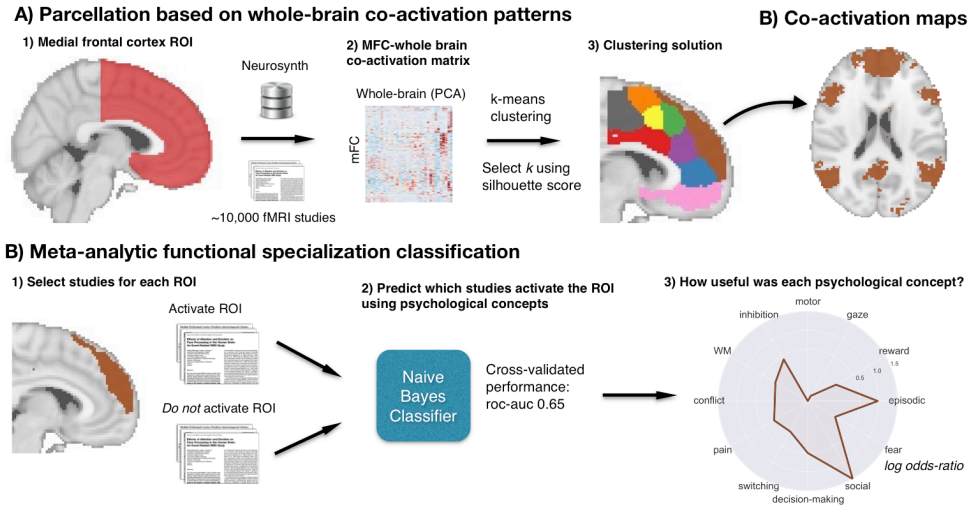


Figure 1. Methods overview. A) Whole brain co-activation of MFC voxels was calculated and k-means clustering was applied resulting in spatially distinct clusters. B) For each cluster, threshold whole-brain co-activation maps were generated C) We functionally characterized each cluster by determining which cognitive functions best predicted their activation.

Functionally separable components of medial frontal cortex

We identified spatially dissociable regions on the basis of shared co-activation profiles with the rest of the brain (25, 27, 28), an approach that exploits the likelihood of a voxel co-activating with another voxel across studies in the meta-analytic database. Because structure-to-function mappings can be identified at multiple spatial scales, we iteratively extracted 2- through 15-cluster solutions and assessed their validity using the silhouette score—a commonly used measure of inter-cluster coherence. Permutation analyses indicated that the null hypothesis of random clustering could be rejected for all solutions, with silhouette scores reaching local

maxima at 3 and 9 clusters. We focus on these solutions as they provide insight into the functional topography of MFC at two different scales (Fig. 2).

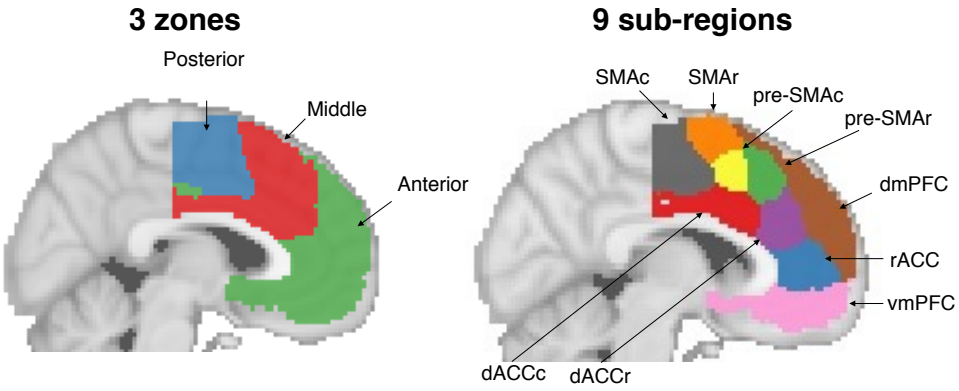


Figure 2. Co-activation-based clustering of MFC at two levels of granularity. A) Three broad functional zones along a rostral-caudal axis. B) Nine-subregions hierarchically organized within the zones. SMA: supplementary motor area; dACC: dorsal anterior cingulate cortex; rACC: rostral anterior cingulate cortex; mPFC: medial prefrontal cortex; dmPFC: dorsal medial PFC; vmPFC: ventromedial PFC. r and c indicate rostral and caudal.

At the coarsest level, MFC divided into three broad bilateral zones organized along the rostral-caudal axis, despite no spatial constrains imposed on the k-means algorithm. We refer to these as the posterior, middle and anterior zones. The posterior zone encompassed the paracentral lobule, SMA, and dorsal posterior midcingulate cortex; the middle zone included portions of pre-SMA as well as much of dorsal anterior cingulate (dACC) running along the corpus callosum (9) an the anterior zone encompassed much of medial prefrontal cortex, including rostral and subgenual ACC, and medial orbitofrontal cortex (OFC).

The nine-cluster solution revealed additional fine-grained topographical organization, with each of the three major zones fractionating in an orderly way into 2-4 smaller regions (84% of all voxels within each zone overlapped with its putative subregions). The resulting sub-regions were generally consistent with extensive cytoarchtechtonic work. Within the posterior zone, we identified two clusters consistent with rostral and caudal SMA (29). Within the middle functional zone, we identified two clusters dorsal to the cingulate sulcus consistent with pre-SMA (30) and two ventral clusters consistent caudal and rostral dACC (9). Within the anterior zone, we identified a rostral ACC cluster that delineated from ventral mPFC (vmPFC) (9) and a dorsal mPFC (dmPFC) cluster which included medial aspects of the frontal pole and superior frontal gyrus. Thus, the boundaries of the clusters we identified using a strict functional co-activation based approach converged with many distinctions previously drawn on the basis of anatomical criteria.

Meta-analytic co-activation profiles

Thus far, we have demonstrated that MFC can be parcellated into robust, anatomically sensible subregions on the basis of meta-analytic co-activation. To better understand the nature of these divisions, we extracted brain-wide co-activation networks for each cluster, providing insight into which functional networks each of these subdivisions reliably participated in. First, we mapped the co-activation patterns of the three functional zones, controlling for co-activation in other zones (Fig. 3A). The posterior zone showed bilateral co-activation with primary motor cortex (PMC) and superior parietal cortex (SPC), anterior cerebellum, and posterior insula (pIns) as well subcortical regions such as the thalamus and putamen—a co-activation pattern consistent with motor function. The co-activation pattern for the middle zone resembled an anterior-shifted version of the posterior zone's pattern, robustly co-activating with more anterior aspects of the

thalamus, as well as regions in the frontoparietal control network such as dorsolateral prefrontal cortex (DLPFC), anterior insula (aIns) and SPC. Finally, the anterior zone showed a qualitatively different pattern, co-activating with default network regions such as angular gyrus, hippocampus and posterior cingulate cortex (PCC) (31). The anterior zone also showed strong co-activation with subcortical regions important for affect-- the amygdala and ventral striatum (VS).

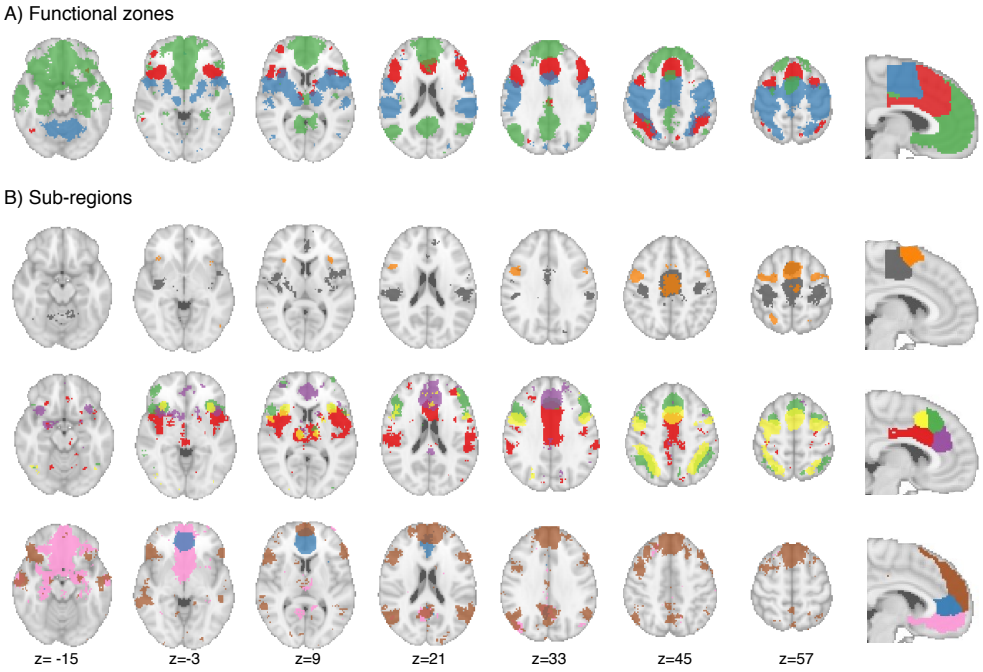


Figure 3. Functional co-activation networks of MFC zones (A) and sub-regions within each zone (B). We determined which voxels across the brain indicated a high probability that each cluster was active, controlling for other clusters in the same map. The three zones showed distinct co-activation patterns while sub-regions within each zone showed fine-grained co-activation

differences. Images are presented using neurological convention and were whole-brain corrected using false detection rate at $p < 0.01$.

To understand the differences in co-activation found within each zone, we calculated co-activation networks for each sub-region controlling for co-activation in other sub-regions in the same zone (Fig. 3B). In the posterior zone, caudal SMA showed greater co-activation with somatosensory cortices and pIns while rostral SMA showed greater co-activation with posterior DLPFC, including the inferior frontal junction (IFJ), as well as aIns— regions associated with goal-directed cognition (28, 32).

Within the middle zone, we found that all four sub-regions strongly co-activated with various aspects of the insula. However, caudal dACC more strongly co-activated with pIns as well as SII and the brain stem—important regions for pain processing (9, 11). In contrast, rostral dACC co-activated more strongly with ventral aIns, as well as lateral OFC—regions previously associated with chemosensory processing (33, 34) and reward-driven learning (35). In contrast, both caudal and rostral pre-SMA were strongly associated with dorsal aIns, in addition to frontoparietal control regions (e.g DLPFC, SPC). However, rostral pre-SMA's co-activation extended anteriorly into the frontal pole, whereas caudal pre-SMA more strongly co-activated with motor cortices, suggesting that these regions are involved at different levels of abstraction in cognitive control.

Within the anterior zone, rACC did not show many co-activation differences from its neighbors, indicating rACC's co-activation pattern is similar to that of the anterior zone as a whole. Surprisingly, both dmPFC and vmPFC showed greater co-activation with PC – a key default network region. In addition, dmPFC robustly co-activated with portions of the so-called

'mentalizing' network, such as the tempo-parietal junction (TPJ) (36) and superior temporal sulcus (STS) (37), as well as lateral PFC, including inferior and middle frontal gyri. Finally, vmPFC showed strong co-activation with subcortical regions, including VS and the amygdala, extending into the hippocampus. As a whole, these co-activation patterns demonstrate that the regions we've identified are involved with distinct functional networks, and suggest that there are likely broad functional differences across MFC zones and accompanied by fine-grained differences within each zone.

Meta-analytic functional specialization

To test if MFC zones and sub-regions exhibited distinct functional specialization, we used a data-driven approach that surveyed a broad range of psychological states to identify those significantly predictive of their activation. For each cluster, we trained a multivariate classifier to predict which studies activated the cluster using a set of 34 psychological concepts derived by applying a standard topic modeling approach to the text of articles in the database (38) (See Table S1 for list of topics). From the resulting fitted classifiers, we calculated the extent to which each psychological concept predicted activity in each cluster and restricted interpretation to significant associations ($p<0.001$) using permutation testing.

Across the three broad MFC zones, we observed distinct functional patterns, consistent with their divergent patterns of functional co-activation (Fig. 4). The posterior zone was primarily involved with motor function, including gaze, consistent with its co-activation with motor regions. The middle zone was primarily associated with various facets of cognitive control, but was also predicted by affective processing, such as pain, reward, decision-making. Consistent with its distinct pattern of co-activation, the anterior zone showed a distinct shift away from

goal-directed cognition and was strongly associated with affective processes, such as reward, fear and decision-making, as well as social processing.

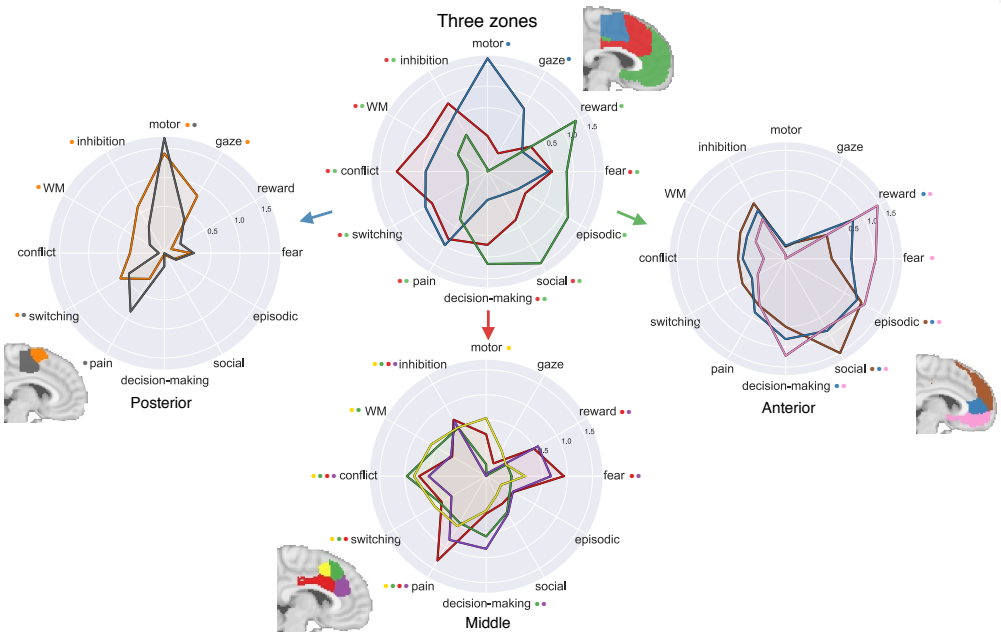


Figure 4. Functional specialization profile of MFC clusters. Each cluster was profiled to determine which psychological concepts best predicted its activation. Top) Each of the three functional zones we identified showed distinct functional profiles with broad shifts across cognitive domains Bottom) Within each zone, sub-regions showed fine-grained shifts in functional. Strength of associations is measured in log-odds ratio and permutation test based significance at $p<0.0001$ is indicated next to each psychological concept by color-coded dots corresponding to each region.

Inspection at a finer spatial scale revealed that sub-regions within each zone showed more subtle shifts in function, similar to the fine-grained shifts in co-activation previously observed. In the posterior zone, activity in both clusters was similarly predicted by motor function and switching. However, only caudal SMA was associated with pain, while rostral SMA showed significant associations with working memory (WM), inhibition and gaze function. In the middle zone, activity in all four sub-regions was significantly predicted by some aspects of cognitive control (conflict and inhibition) and pain, although only activity in pre-SMA was significantly predicted by WM. dACC clusters were further characterized by a strong association with affect-- including fear and reward. In addition to differences between pre-SMA and dACC, we also found that only activity in caudal pre-SMA was predicted by motor function, while activity in rostral pre-SMA and dACC was predicted by decision-making.

In the anterior zone, activity in all three sub-regions was significantly predicted by episodic memory and social processing; however, the association with social processing peaked in dmPFC, consistent with a previous meta-analysis (18). In contrast, the reverse was true for reward and decision-making: only activity in rACC and vmPFC was significantly by these processes. Moreover, fear was maximally associated with vmPFC, consistent with its strong co-activation with the amygdala. Interestingly, however, no region in the anterior zone was significantly associated with pain processing, suggesting fear and pain have dissociable associations in MFC.

Functional complexity

Thus far, we have functionally characterized MFC subregions by determining which psychological concepts are most predictive of their activity. However, we were also interested in

determining how broadly or specifically each region was associated to different cognitive processes. We approached this problem by determining the number of psychological concepts that were required to maximally predict activity in each MFC sub-region, reasoning that if a region's activity can be explained with less psychological concepts, it indicates it is associated with less functions. For each region individually, we retrained our naïve Bayes classifier using only a single cognitive concept and subsequently added new concepts into the model one by one, ordered by their usefulness in classification. Not surprisingly, across all sub-regions, performance increased as a function of the number of psychological concepts in the model, reaching peak performance (receiver operating characteristic area under the curve (ROC-AUC): 0.62) with 23.8 functions on average.

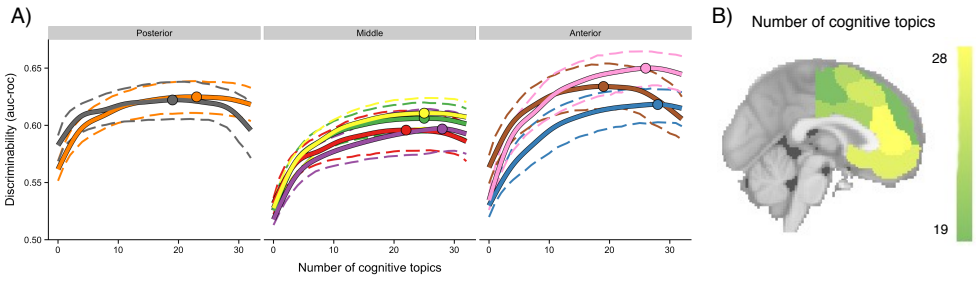


Figure 5. Functional complexity of MFC. (A) As the number of cognitive functions in the classifier increased (x-axis) discriminability of activity (y-axis) increased for all regions. However, regions varied in the number of topics required to reach maximum discriminability (noted by a circle). Bootstrapped 95% confidence intervals are shown for each region using dotted lines. B) We plotted the average number of topics needed to reach maximum discriminability on a sagittal brain slice. Rostral dACC and rostral ACC required the most

psychological concepts to maximally discriminate their activation, while dmPFC and caudal SMA required the least.

However, MFC regions varied in two key aspects of these metrics: maximum discriminability, and the number of topics required to reach this maximum. The maximum discriminability reflects how well overall a region's function is explained by the psychological concepts we employed and the number of topics required to reach this maximum reflects the complexity of function observed in each region. Regions in the middle functional zone reached generally lower discriminability, likely because these regions have a high rate of activation across many tasks. Conversely, regions in mPFC, and in particular vmPFC, reached greater level of discriminability, suggesting that the psychological concepts we used encompassed their function well.

Regions in MFC varied in the number of topics required to reach the maximum discriminability level, a property we termed 'functional complexity' (Fig. 5B). Caudal SMA required the fewest number of topics to reach its modest maximum discriminability level; in fact, we are able to discriminate activity in caudal SMA well above chance using only a single topic: motor function. At the other end of the spectrum, rACC and rostral dACC required a greater number of topics to reach maximum discriminability, suggesting a complex model of cognitive function is required to accurately predict the activity of these regions. Surprisingly, the two regions with the highest activation base rate, rostral and caudal pre-SMA, did not show the highest functional complexity. In fact, base rate of activation was not significantly correlated with functional complexity across MFC ($r = 0.24$). These findings suggest that highly active areas of MFC in the middle functional zone may not in fact be involved with a wide variety of functions, but instead may a smaller set of functions that are often used in a variety of behaviors.

Discussion

In the current study, we identified and functionally characterized separable regions of the medial frontal cortex by applying a data-driven approach to a large-scale database of ~10,000 fMRI studies. We identified three broad zones arranged along the rostra-caudal axis with distinct patterns of whole-brain co-activation and functional specialization. These zones further fractionated into 2-4 subregions consistent with cytoarchitechtonic parcellations that showed more fine-grained shifts in both co-activation and function. Furthermore, we quantified the functional complexity in each of these sub-regions and found that regions previously hypothesized to show high diversity, such as dACC, only showed moderate heterogeneity. Below, we discuss the implications of our results for each zone individually.

Posterior zone

The posterior MFC zone spanned regions previously associated with motoric function--such as SMA-- and delineated from pre-SMA, in a manner consistent with cytoarchtonics (9, 29) and rs-fMRI connectivity (39). Thus, it follows this zone was primarily associated with motor function and co-activated with key motor regions such as primary motor cortex and thalamus. However, our results suggest that posterior MFC can be further fractionated into caudal and rostral sub-regions that specialize in different aspects of motor function. Caudal SMA showed a greater assocation with pain processing, as well as co-activation with other key pain regions such as SII and thalamus (11). Given that pain signals often indicate the need for motor action to avoid damage to the organism, caudal SMA may be particularly specialized in initiating such reflexive movements in response to pain. In contrast, rostral SMA was implicated in various aspects of executive function and co-activated with regions in the fronto-parietal control system such as rostral DLPFC and aIns. These results are consistent with the well-established finding

that the supplementary eye fields, are important for high-level control of eye movements in tasks such as anti-saccade (40, 41). While rostral SMA is unlikely to be involved in the resolution of conflict or direct maintenance of WM, the direct cortico-spinal connections in this region (42) suggest it is well situated to modify motor action to support goal-directed cognition.

Middle zone

The middle MFC zone was associated with a variety of cognitive control in addition to negative affect. At a coarse scale, these findings seem consistent with recent hypotheses suggesting that "dorsal ACC" is important for the integration of negative affect into cognitive control processes (20). Upon closer inspection, however, we observed substantial functional-anatomical specificity. We identified four sub-regions with dissociable whole-brain co-activation: caudal and rostral pre-SMA and caudal and rostral dACC. These sub-regions are consistent with evidence suggesting caudal dACC and rostral dACC show distinct cellular organization and demarcate from pre-SMA along the cingulate sulcus (9). We found that although all four regions co-activated with regions important for goal-driven cognition, such as aIns and DLPFC, the two pre-SMA subregions show greater co-activation with these regions and stronger associations with several aspects executive function-- in particular WM. In contrast, activity in dACC clusters was more strongly associated with affective processes-- including fear, reward and pain. These functional distinctions may only be appreciable using analytical methods that appropriately control for the high base rate of activation of this region (24).

These functional dissociations suggest that existing models of cognitive control may underspecify the functional topography of middle MFC. In particular, some influential theories of cognitive motoric control consider dACC to be the region primarily responsible for conflict

processing. However, our results suggest that human conflict-related activity, in addition to other executive processes are most associated pre-SMA proper. Our findings are consistent with previously raised concerns that macaques primarily show conflict related activity in pre-SMA and not dACC (43, 44). Our results support an alternate hypothesis in which negative affective signals that indicate possible conflict may be initially processed in dACC – consistent with this region's known direct cortico-spinal connections -- but these signals may only be integrated with high-level goals in pre-SMA.

We also found evidence that the two sub-regions of dACC specialized in different types of affective processes. Caudal dACC was more strongly associated with pain, consistent with co-activation with regions in the pain matrix (11), while rostral dACC was more strongly associated with decision-making and reward, consistent with greater co-activation with regions important for reward, such as the VS and lateral OFC (35, 45). Notably, rostral pre-SMA was also associated with decision-making and showed co-activation lateral OFC. These results are consistent with existing hypotheses that conflict adaptation may be dependent on learning-processes to avoid future negative outcomes (8).

Anterior zone

Anterior MFC showed a distinct pattern of functional specialization from the rest of MFC, showing low associations with motor and executive functions and strong associations with affect, decision-making, social cognition, and episodic memory. This was accompanied by a distinct pattern of whole-brain co-activation, primarily with regions of the default network, such as PCC, hippocampus as well as sub-cortical regions such as amygdala and VS. These results are

consistent with claims that mPFC is a key region of the 'default network' (31)—a network specialized in internally oriented processes.

However, anterior MFC is not a unitary area and fractionated into three subregions: dmPFC, rACC and vmPFC. dmPFC was the most strongly associated with social processing, consistent with several studies linking dmPFC to social perception and self-referential thought (46). Moreover, dmPFC showed strong co-activation with TPJ, a region thought to also be important for mentalizing (17, 18). Importantly, dmPFC showed very low association with reward processing, suggesting that higher-level mentalizing processes occur separately from low-level affective processing. Rostral ACC showed a less specific functional pattern, consistent with the high functional complexity we observed. rACC was moderately associated with a variety of including low-level affective processes, such as fear and reward, and higher-level processes such as decision-making. These findings are consistent with descriptions of the existence of a default network 'hub' region in mPFC (47, 48). As a hub of the default network, rACC is likely to be involved in many of the processes supported by this network, but not be specialized in any given process.

Finally, our results suggest that vmPFC is primarily associated with low-level affective processes, such as reward and fear. This is consistent with vmPFC's robust co-activation with subcortical regions, such as VS (49) and amygdala (50) , respectively. Importantly, although some have characterized vmPFC as being a 'valuation' system (51), these results suggest that this region is equally important for processes more closely related with the amygdala and related negative emotions. Thus vmPFC may play a general role incorporating a variety of affective signals into cortex, while more dorsal regions, such as rACC may be important for integrating or contextualizing these signals with the rest of the default network (52).

While our large-scale meta-analytic approach allowed us to comprehensively synthesize a plethora of fMRI findings, there are several limitations. First, the topic modeling approach we employ is data-derived from the semantic content of papers, and thus is not driven by theoretical models that may be critical for discriminating the activity of certain regions. Although this topic model provides a substantial improvement over term based meta-analysis (38), these topics are still based purely on the frequency that terms appear in the body of fMRI studies and are not able to capture more complex syntactic structures which may denote fine-grained functional. Second, the quality of activation data in Neurosynth is inherently limited due to its automatically generated nature; for example, the Neurosynth parser does not distinguish between activations and deactivations, nor does it distinguish different tables within an article that may report different contrasts. However, previous validation analyses have shown that these limitations are unlikely to contribute systematic biases to the data and primarily reduce the overall spatial fidelity (24). Thus, the large-scale nature of the current meta-analysis (N= 9,721) helps ameliorate the additional noise introduced by this approach. Future application of more sophisticated data-mining techniques on the activation extraction and semantic annotation may improve this situation.

Moreover, as with any meta-analysis of fMRI data, our approach is limited by the low spatial resolution of fMRI and the inability to disentangle individual differences in anatomy across subjects. In particular, it is difficult to precisely localize each of our clusters onto gyri and sulci; this is particularly problematic in dACC, where BA 32' lies only a few millimeters dorsal of BA 24, and shows large anatomical variation across humans (44, 53). While only advances in radiology will improve spatial resolution, the open sharing of low-level fMRI data will enable meta-analyses with subject-specific anatomical registration. The benefit of open data sharing will

be compounded if these datasets are accompanied by high-quality ontological metadata (e.g. expert knowledge) that is otherwise difficult to ascertain.

In conclusion, we used meta-analytic co-activation to identify three broad functional zones along a rostro-caudal axis in MFC that functionally mapped on to distinct cognitive domains. Within each of these zones, we identified component sub-regions with distinct patterns of whole-brain co-activation and discovered appreciable amount of fine-grained functional specialization. Our analyses suggest that integrative accounts of MFC function may be overstated and result from not controlling for variation in activation base rate across the brain.

Materials and Methods

Neuroimaging Database

We analyzed the Neurosynth database (24), a repository of 9,721 fMRI studies and over 350,000 activations. Each observation contains the peak activations for all contrasts reported in a study's table as well as the frequency of all of the words in the article abstract. Activations are smoothed using a 6mm Gaussian kernel.

Co-activation clustering

We clustered individual voxels inside of a MFC mask based on their co-activation with voxels in the rest of the brain. First, we defined a ROI in Montreal Neurological Institute (MNI) space using FSLView by excluding all voxels further than 10mm from the midline of the brain, voxels posterior to central sulcus ($Y < -22$) and voxels ventral to vmPFC ($Z < -32$). Next, we removed voxels with low grey matter signal by excluding voxels with less than 30% probability of being grey matter according to the Harvard-Oxford anatomical atlas and very low activation in

the database (less than 80 studies per voxel). Next, we calculated the correlation between each MFC voxel with the rest of the brain across studies. As this would result in a very large matrix that would be computationally intractable to cluster, we reduced the dimensionality of the rest of the brain using principal components analysis (PCA). We applied PCA to the matrix containing activation of every voxel in the brain across all studies (228453 voxels x 9721 studies) to reduce it to 100 components (100 voxels x 9721 studies). Then, we computed the correlation distance of between every voxel in the MFC ROI with each PCA component resulting in a matrix of distance between MFC voxels. We applied k-means clustering to this matrix, as this algorithm is computationally efficient, commonly used, and shows high goodness of fit and reproducibility (54). We used the k-means++ initialization procedure, ran the algorithm 10 times on different centroid seeds and selected the best output of these consecutive runs in terms of inertia to avoid local minima. The algorithm was run on different k values, resulting in solutions for 2 to 15 regions.

Since the optimality of a given clustering depends in large part on investigators' goals, the preferred level of analysis, and the nature and dimensionality of the available data, identifying the 'correct' number of clusters is arguably an intractable problem (55). However, in the interest of pragmatism, we attempted to objectively select the number of clusters using the silhouette score, a measure of within-cluster cohesion. The silhouette coefficient was defined as $(b - a) / \max(a, b)$, where a is the mean intra-cluster distance and b is the distance between a sample and the nearest cluster that the sample is not a part of. Solutions that minimized the average distance between voxels within each cluster received a greater score. Because it is unclear what should be considered a significant silhouette score, we used a permutation procedure previously employed by our group (56) to infer if a given clustering solution was warranted. For each possible

solution between 2 and 15 clusters, we permuted the data matrix generating a new permuted data set with no relationship between voxels. We then re-applied the clustering algorithm, and re-calculated the silhouette score 1000 times resulting in a null-hypothesis distribution of silhouette scores for each *k*. We used this null distribution to calculate z-scores for each solution and select solutions for further analysis.

Co-activation profiles

Alejandro De La Vega 9/22/2015 4:49 PM
Comment [2]: Is this enough detail? I'm trying to save space

To determine which voxels across the brain co-activated with each MFC parcel, we performed a meta-analysis resulting in whole-brain maps that indicate which voxels across the brain are active in the studies that activated each parcel. To display the unique co-activation of each region, we controlled for the co-activation of other parcels in the same map by performing a meta-analysis on studies that uniquely activated each ROI, and excluded studies that also activated other parcels (e.g. only studies that activated anterior MFC, and not middle or posterior MFC). For each voxel across the brain, we calculated the conditional probability of activation across the selected set of studies and calculated p-values for each voxel using a wwo-way chi-square test. Next, we thresholded significant voxels using False Discovery Rate correction at $p < 0.01$ and binaries the resulting maps for display. We create co-activation maps using the NiLearn library for Python.

Topic modeling

Although term-based meta-analysis maps in Neurosynth closely resemble the results of manual meta-analyses of the same concepts, there is a high degree of redundancy between terms (e.g. 'episodes' and 'episodic') and potential ambiguity as to the meaning of an individual word out of context (e.g. 'memory' can indicate working memory or episodic memory). To remedy

this, we employed a reduced semantic representation of the latent conceptual structure underlying the neuroimaging literature: a set of 60 topics derived using latent dirichlet allocation topic-modeling. This procedure was identical to that used in a previous study (57), except for the use of a smaller number of topics and a much larger version of the Neurosynth database. The generative topic model derives 60 independent topics from the co-occurrence across studies of all words in the abstracts fMRI studies in the database. Each topic loads onto individual words to a varying extent, facilitating the interpretation of topics; for example, a working memory topic loads highest on the words 'memory, WM, load', while an episodic memory topic loads on 'memory, retrieval, events'. Note that both topics highly load on the word “memory”, but the meaning of this word is disambiguated because it is contextualized by other words that strongly load onto that topic. Out of the 60 generated topics, we excluded 25 topics representing non-psychological phenomena-- such as the nature of the subject population (e.g. gender, special populations) and methods (e.g., words such as “images”, “voxels”)—resulting in 35 psychological concepts.

Meta-analytic functional specialization

We generated functional profiles of MFC regions by determining which psychological topics best predicted each MFC region’s activity across fMRI studies. First, we selected two sets of studies: studies that activated a given parcel--defined as activating at least 5% of voxels in the parcel-- and studies that did not--defined as activating no voxels in the parcel. For each parcel, we trained a naive Bayes classifier to discriminate these two sets of studies based on psychological concepts herein. We chose naive Bayes because we have previously had success applying this algorithm to Neurosynth data (24), these algorithms perform well on many types of data (58) and equire almost no tuning of parameters to achieve a high level of performance.

We assessed our models' ability to predict if an unseen study activated a region, given the content of the study. In other words, if we know what cognitive topic a study is about, how well can we predict if it activates a specific region? We used 4-fold cross validation for testing and calculated the he mean score across all folds as the final measure of performance. We scord our models using the receiver operating characteristic (AUC-ROC) --a summary metric of classification performance that take into account both sensitivity and specificity – because this measure is not detrimentally affected by unbalanced data. This was important because each region varied in the ratio of studies that activated it to the studies that did not.

To generate functional specialization profiles, we extracted from the naive Bayes models the log odds-ratio of a feature being present in active studies versus inactive studies, defined as the log of the ratio between the mean loading of each cognitive concept in studies that activated a given region to the mean loading in studies that did not activate he ratio. Log odds-ratio values above 0 indicate that a cognitive concept is predictive of activation of a given region. To determine the significance of these associations, we permuted the class labels indicating if a study activated a region and extracting the log odds-ratio for each cognitive concept, 1000 times. This resulted in a null distribution of log odds-ratio for each cognitive concept and each region. Using this null distribution, we calculated p-values for each pairwise relationship between psychological concepts and regions and indicated significant associations at the $p<0.001$ threshold.

Functional complexity

We quantified the complexity of function in order to determine if MFC regions are involved in a diverse range of cognitive functions. We operationalized regions with heterogenous function as those that required a larger number of topics to accurately predict their activity, while regions

with more homogenous function are those that would require fewer topics to correctly classify. We started by fitting the simplest possible model and attempting to predict activity for each region only using the topic that had the greatest weight in the complete model. We then assessed the benefit of including additional topics by sequentially adding topics as predictors (up to 35) to the model in order of their importance in the full model. This processes was repeated 1000 times with data resampled without replacement (bootstrapping) to account for sampling error.

Scikit-learn (59), a Python machine learning module, was used for all machine learning analyses in this study.

Acknowledgments

R01MH096906 National Institutes of Health.

References

1. Leek EC, Johnston SJ (2009) Functional specialization in the supplementary motor complex. *Nat Rev Neurosci*.

2. Roland PE, Larsen B, Lassen NA (1980) Supplementary motor area and other cortical areas in organization of voluntary movements in man. *Journal of …*.

3. Kennerley SW, Sakai K (2004) Organization of action sequences and the role of the pre-SMA. *Journal of …*. doi:10.1152/jn.00651.2003.

4. Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999) Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402(6758):179–181.

5. Milham MP, et al. (2001) The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on nature of conflict. *Cognitive Brain Research* 12(3):467–473.

6. Rushworth M, Walton ME, Kennerley SW (2004) Action sets and decisions in the medial frontal cortex. *Trends in cognitive …*. doi:10.1016/j.tics.2004.07.009.

7. Holroyd CB, Nieuwenhuis S, Yeung N (2004) Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. *Nature*.

8. Brown JW, Braver TS (2005) Learned Predictions of Error Likelihood in the Anterior Cingulate Cortex. *Science* 307(5712):1118–1121.

9. Vogt BA (2005) Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci* 6(7):533–544.

10. Rolls ET, et al. (2003) Representations of Pleasant and Painful Touch in the Human Orbitofrontal and Cingulate Cortices. *Cerebral Cortex* 13(3):308–317.

11. Wager TD, et al. (2013) An fMRI-Based Neurologic Signature of Physical Pain. *N Engl J Med* 368(15):1388–1397.

12. Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences* 4(6):215–222.

13. Lindquist KA, Wager TD, Kober H, Bliss-Moreau E, Barrett LF (2012) The brain basis of emotion: A meta-analytic review. *Behavioral and Brain Sciences* 35(03):121–143.

14. Critchley HD, et al. (2003) Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* 126(10):2139–2152.

15. Rogers RD, et al. (2004) Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-

making cognition. *Biological Psychiatry* 55(6):594–602.

16. Hare TA, Camerer CF, Rangel A (2009) Self-Control in Decision-Making Involves Modulation of the vmPFC Valuation System. *Science* 324(5927):646–648.

17. Baumgartner T, Götte L, Gügler R, Fehr E (2012) The mentalizing network orchestrates the impact of parochial altruism on social norm enforcement. *Hum Brain Mapp* 33(6):1452–1469.

18. Denny BT, Kober H, Wager TD, Ochsner KN (2012) A Meta-analysis of Functional Neuroimaging Studies of Self- and Other Judgments Reveals a Spatial Gradient for Mentalizing in Medial Prefrontal Cortex. *http://dxdoiorg/101162/jocn_a_00233* 24(8):1742–1752.

19. Spreng RN, Grady CL (2010) Patterns of Brain Activity Supporting Autobiographical Memory, Prospection, and Theory of Mind, and Their Relationship to the Default Mode Network. *http://dxdoiorg/101162/jocn200921282* 22(6):1112–1123.

20. Shackman AJ, et al. (2011) The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci* 12(3):154–167.

21. Palomero-Gallagher N, et al. (2015) Functional organization of human subgenual cortical areas: Relationship between architectonical segregation and connectional heterogeneity. *NeuroImage* 115(C):177–190.

22. Poldrack RA (2006) Can cognitive processes be inferred from neuroimaging data? *Trends in Cognitive Sciences*. doi:10.1016/j.tics.2005.12.004.

23. Nelson SM, et al. (2010) Role of the anterior insula in task-level control and focal attention. *Brain Structure and Function* 214(5-6):669–680.

24. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD (2011) Large-scale automated synthesis of human functional neuroimaging data. *Nat Meth* 8(8):665–670.

25. Toro R, Fox PT, Paus T (2008) Functional Coactivation Map of the Human Brain. *Cerebral Cortex* 18(11):2553–2559.

26. Robinson JL, Laird AR, Glahn DC, Lovallo WR, Fox PT (2010) Metaanalytic connectivity modeling: Delineating the functional connectivity of the human amygdala. *Hum Brain Mapp* 31(2):173–184.

27. Smith SM, et al. (2009) Correspondence of the brain's functional architecture during activation and rest. *PNAS* 106(31):13040–13045.

28. Chang LJ, Yarkoni T, Khaw MW, Sanfey AG (2013) Decoding the Role of the Insula in Human Cognition: Functional Parcellation and Large-Scale Reverse Inference. *Cerebral Cortex* 23(3):739–749.

29. Vorobiev V, Luppino G (1998) Parcellation of human mesial area 6: cytoarchitectonic evidence for three separate areas. 1–5.

30. Picard N, Strick PL (1996) Motor Areas of the Medial Wall: A Review of Their Location and Functional Activation. *Cerebral Cortex* 6(3):342–353.

31. Andrews-Hanna JR (2012) The Brain's Default Network and Its Adaptive Role in Internal Mentation. *The Neuroscientist* 18(3):251–270.

32. Nelson SM, et al. (2010) Role of the anterior insula in task-level control and focal attention. *Brain Structure and Function* 214(5-6):669–680.

33. Yaxley S, Rolls ET, Sienkiewicz ZJ (1990) Gustatory responses of single neurons in the insula of the macaque monkey. *Journal of Neurophysiology* 63(4):689–700.

34. Rolls ET, Yaxley S, Sienkiewicz ZJ (1990) Gustatory responses of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. *Journal of Neurophysiology* 64(4):1055–1066.

35. Schoenbaum G, Roesch M (2005) Orbitofrontal Cortex, Associative Learning, and Expectancies. *Neuron* 47(5):633–636.

36. Carter RM, Huettel SA (2013) A nexus model of the temporal–parietal junction. *Trends in Cognitive Sciences* 17(7):328–336.

37. Zilbovicius M, et al. (2006) Autism, the superior temporal sulcus and social perception. *Trends in Neurosciences* 29(7):359–366.

38. Poldrack RA, et al. (2012) Discovering Relations Between Mind, Brain, and Mental Disorders Using Topic Mapping. *PLoS Comput Biol* 8(10):e1002707.

39. Kim J-H, et al. (2010) Defining functional SMA and pre-SMA subregions in human MFC using resting state fMRI: Functional connectivity-based parcellation method. *NeuroImage* 49(3):2375–2386.

40. Corbetta M, Akbudak E, Conturo TE, Snyder AZ (1998) A common network of functional areas for attention and eye movements. *Neuron* 21(4):761–773.

41. Everling S, Munoz DP (2000) Neuronal Correlates for Preparatory Set Associated with Pro-Saccades and Anti-Saccades in the Primate Frontal Eye Field. *Journal of Neuroscience* 20(1):387–400.

42. Luppino G (1993) Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. 1–27.

43. Nakamura K, Roesch MR (2005) Neuronal activity in macaque SEF and ACC during performance of tasks involving conflict. *Journal of …*.

44. Cole MW, Yeung N, Freiwald WA, Botvinick M (2009) Cingulate cortex: Diverging data from humans and monkeys. *Trends in Neurosciences* 32(11):566–574.

45. Elliott R, Dolan RJ, Frith CD (2000) Dissociable Functions in the Medial and Lateral Orbitofrontal Cortex: Evidence from Human Neuroimaging Studies. *Cerebral Cortex* 10(3):308–317.

46. Mitchell JP, Banaji MR, Macrae CN (2006) The Link between Social Cognition and Self-referential Thought in the Medial Prefrontal Cortex. *http://dxdoiorg/101162/0898929055002418* 17(8):1306–1315.

47. van den Heuvel MP, Sporns O (2013) Network hubs in the human brain. *Trends in Cognitive Sciences* 17(12):683–696.

48. Andrews Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL (2010) Functional-Anatomic Fractionation of the Brain's Default Network. *Neuron* 65(4):550–562.

49. Knutson B, Adams CM, Fong GW, Hommer D (2001) Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*.

50. Phillips RG, LeDoux JE (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behavioral Neuroscience* 106(2):274–285.

51. Lebreton M, Jorge S, Michel V, Thirion B, Pessiglione M (2009) An Automatic Valuation System in the Human Brain: Evidence from Functional Neuroimaging. *Neuron* 64(3):431–439.

52. Roy M, Shohamy D, Wager TD (2012) Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends in Cognitive Sciences* 16(3):147–156.

53. Paus T (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. 1–8.

54. Thirion B, Varoquaux G, Dohmatob E, Poline J-B (2014) Which fMRI clustering gives good brain parcellations? *Frontiers in Neuroscience* 8. doi:10.3389/fnins.2014.00167.

55. Poldrack RA, Tal Yarkoni (2016) From Brain Maps to Cognitive Ontologies: Informatics and the Search for Mental Structure. *Annual Review of Psychology*.

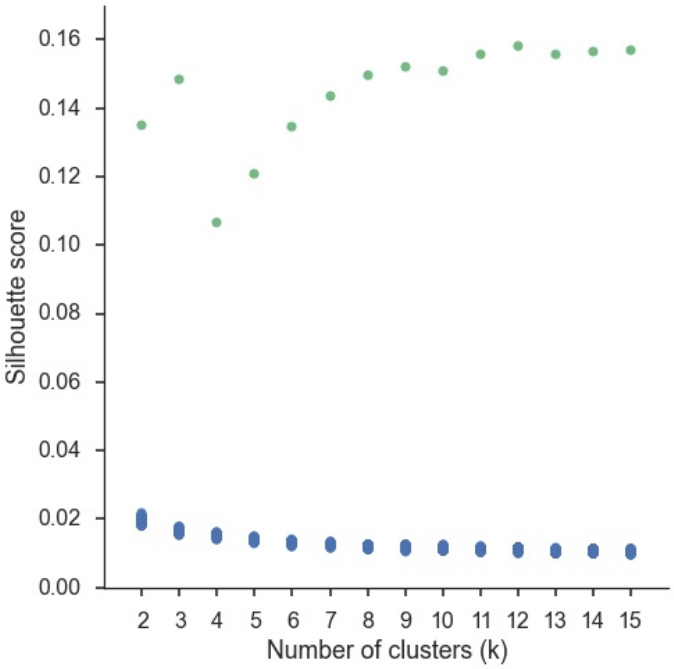
56. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN (2008) Prefrontal-Subcortical Pathways Mediating Successful Emotion Regulation. *Neuron* 59(6):1037–1050.

57. Poldrack RA, et al. (2012) Discovering Relations Between Mind, Brain, and Mental Disorders Using Topic Mapping. *PLoS Comput Biol* 8(10):e1002707.

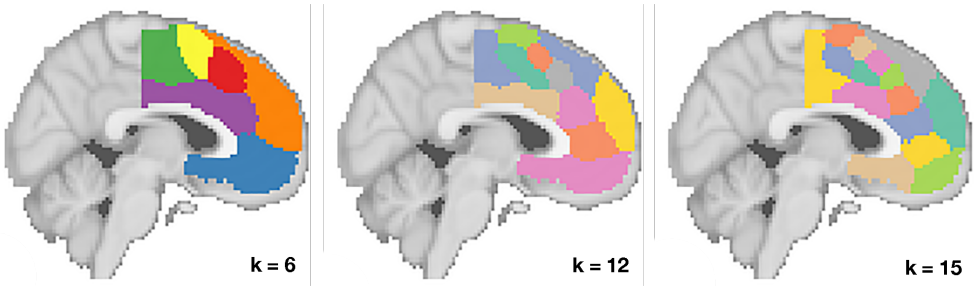
58. Androutsopoulos I, Koutsias J, Chandrinos KV, Paliouras G, Spyropoulos CD (2000) An evaluation of Naive Bayesian anti-spam filtering.

59. Pedregosa F, et al. (2011) Scikit-learn: Machine Learning in Python. *Journal of Machine Learning Research* 12(Oct):2825–2830.

Supporting Information



Supplemental Figure 1. Silhouette scores of real (green) and permuted (green) clustering solutions (green). Clustering was performed on permuted data 500 times for each k to compute a null distribution. We z-scored real clustering scores and determined they were all significantly greater than chance ($p<.0001$). Silhouette scores reached local maxima at 3, 9 and 12 regions, although silhouette scores only increased slightly after 9 clusters.



Supplemental Figure 2. Clustering solutions for 6, 12, and 15 clusters.

Supplemental Table 1. Topics derived from topic modeling.

Cognitive Concept Topics

Name of topics as given by authors in left columns.

Topic Name	**Five highest loading words**				
stress	stress	awareness	experience	conscious	cortisol
gaze	eye	gaze	movements	eyes	visual
decision-making	decision	choice	risk	decisions	choices
reasoning	reasoning	rule	rules	intelligence	complexity
sensory	visual	auditory	sensory	modality	integration
spatial	spatial	location	mental	space	virtual
repetition priming	repetition	priming	hearing	repeated	suppression
feature detection	visual	category	adaptation	color	features
episodic memory	memory	events	imagery	autobiographical	retrieval
object recognition	object	objects	visual	recognition	familiar
motor function	motor	movement	movements	sensorimotor	primary
attention	attention	attentional	visual	spatial	target
learning	learning	training	performance	practice	sequence
social cognition	social	empathy	moral	person	judgments
tms/stimulation	stimulation	somatosensory	tms	primary	tactile

mathematics	arithmetic	numerical	mental	magnitude	calculation
sentence comprehension	sentences	comprehension	sentence	language	syntactic
reward	reward	anticipation	monetary	responses	rewards
error processing	feedback	error	learning	errors	prediction
switching	cues	target	trials	cue	switching
audition	auditory	speech	sounds	music	sound
emotion	emotional	emotion	negative	neutral	facial
language	language	speech	production	fluency	asymmetry
reading	reading	word	words	phonological	chinese
conflict & interference	conflict	interference	control	incongruent	trials
semantic	semantic	words	word	lexical	knowledge
inhibition	inhibition	control	inhibitory	stop	motor
encoding & retrieval	memory	encoding	retrieval	recognition	episodic
motor action	action	actions	motor	observation	mirror
fear & anxiety	fear	anxiety	threat	responses	conditioning
food	food	taste	body	weight	eating
working memory	memory	performance	cognitive	wm	tasks
motion perception	motion	visual	perception	body	human
pain	pain	painful	stimulation	somatosensory	intensity

Non-Cognitive Topics

Non-cognitive topics were not named, and are instead numbered.

Topic	Top five loading words				
35	women	sex	gender	females	males
36	placebo	pet	tomography	emission	dopamine
37	schizophrenia	controls	risk	reduced	deficits
38	condition	conditions	tasks	control	performance
39	ad	disease	mci	alzheimer	atrophy
40	individuals	cognitive	individual	control	behavioral
41	wm	fractional	integrity	tracts	diffusivity
42	lesions	controls	patient	lesion	stroke
43	human	humans	organization	located	primates
44	network	role	evidence	human	distinct
45	network	resting	default	mode	rest
46	frequency	source	alpha	amplitude	beta
47	pd	controls	disease	clinical	motor
48	disorder	adhd	bipolar	controls	ocd
49	depression	mdd	depressed	disorder	depressive
50	images	standard	time	voxel	image
51	time	sustained	delay	phase	period
52	alcohol	acupuncture	cocaine	users	drug
53	volume	gray	voxel	gm	morphometry

54	effective	causal	network	dynamic	modeling
55	carriers	allele	gene	genotype	genetic
56	ptsd	social	game	attachment	trauma
57	asd	autism	social	reho	controls
58	age	adults	children	adolescents	sleep
59	features	free	sensitivity	classifier	feature
60	responses	stimulus	effect	design	neuronal