Title: Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization

Abbreviated title: Large-scale meta-analysis of medial frontal cortex

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Number of pages: 34

Number of figures: 5

Number of words for abstract: 212

Number of words for introduction: 653

Number of words for discussion: 1424

Conflicts of Interest: The authors declare no competing financial interests.

Acknowledgments: R01MH096906 National Institutes of Health.

Abstract

The human medial frontal cortex (MFC) has been the subject of intense study, having been associated with diverse psychological processes that include motor processing, goal-directed behavior and affect. There is a need for comprehensive efforts to identify functional subregions with distinct functional profiles across these diverse processes. To address this need, we systematically created a functional-anatomical mapping of MFC from a database of nearly 10,000 neuroimaging studies. Using a data-driven approach, we identified putatively separable regions of MFC at several spatial scales on the basis of meta-analytic co-activation, 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 more subtle shifts in co-activation within those networks. Multivariate classification analyses aimed at identifying the psychological concepts most strongly predictive of activity in each region revealed a tripartite division within MFC, with each zone displaying a relatively distinct functional signature; the posterior zone was associated primarily with motor function, the middle zone with cognitive control and negative affect and the anterior with internal mentation and affective processing. Upon closer inspection, we also identified fine-grained shifts in functional specialization within each zone, revealing greater functional diversity than previous "unifying" accounts of MFC might suggest.

Significance Statement

The medial frontal cortex is a cortical area that has been associated with many psychological processes using functional MRI. The high frequency of activation in this area, 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 identified 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) encompasses 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 (Roland et al., 1980; Kennerley and Sakai, 2004; Leek and Johnston, 2009), while nearby dorsal anterior cingulate cortex (ACC) has been implicated in various aspects of cognitive control, such as conflict (Botvinick et al., 1999; Milham et al., 2001; Rushworth et al., 2004) and error processing (Holroyd et al., 2004; Brown and Braver, 2005), and also pain processing (Rolls et al., 2003; Vogt, 2005; Wager et al., 2013). Further anterior, medial prefrontal cortex (mPFC) and subgenual ACC have been shown to be important for a variety of affective processes, including emotion (Bush et al., 2000; Lindquist et al., 2012), autonomic function (Critchley et al., 2003), and valuation (Rogers et al., 2004; Hare et al., 2009). Furthermore, portions of mPFC have also been associated with internally oriented processes, such as mentalizing (Baumgartner et al., 2012; Denny et al., 2012) and autobiographical memory (Spreng and Grady, 2010). Moreover, the functional organization supporting these diverse processes has been investigated using a wide range of methods, including cytoarchitecture (Ongur and Price, 2000; Vogt, 2005), computational models (Alexander and Brown, 2011), network-level descriptions (Andrews Hanna et al., 2010; Power et al., 2011), and theory-driven meta-analyses (Bush et al., 2000; Shackman et al., 2011; Denny et al., 2012).

Despite the enormous amount of research on specific subregions within MFC, there have been few large-scale efforts to comprehensively map the full range of psychological functions onto medial frontal anatomy. Since most researchers tend to be intimately familiar with one particular domain of cognition, most meta-analyses are necessarily restricted to a relatively small

subset of empirical findings relevant to that domain. Even those meta-analyses that attempt to take a broader look at organization of the MFC typically only include a subset of cognitive states hypothesized to be important (e.g. negative affect and cognitive control see Bush et al., 2000; Shackman et al., 2011) or restrict themselves to a small region of interest (e.g. subgenual ACC, see Palomero-Gallagher et al., 2015). Such meta-analyses are 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 (Poldrack, 2006). This concern is particularly acute in the case of pre-SMA and dACC, which are activated in a large proportion of fMRI studies, raising questions about their whether these regions are selectively involved in specific mental functions (Nelson et al., 2010a; Yarkoni et al., 2011).

Here we attempt to overcome these issues by creating a comprehensive mapping between psychological function and MFC anatomy using Neurosynth, a diverse large-scale database of over 10,000 fMRI studies. We first clustered MFC voxels into functionally separable regions at several spatial scales based on their meta-analytic co-activation with the rest of the brain (Toro et al., 2008; Smith et al., 2009; Robinson et al., 2010). This procedure revealed three zones along the rostro-caudal axis that further fractionated into nine sub-regions. In contrast to cytoarchitechtonic (Vorobiev and Luppino, 1998; Vogt, 2005; Palomero-Gallagher et al., 2013) and connectivity based parcellations (Beckmann et al., 2009; Neubert et al., 2015) – which delineate regions on the basis of static anatomical properties—the present analysis identified clusters with distinct signatures of functional activation across a wide range of psychological manipulations. We then characterized each cluster's psychological profiles using multivariate classification and found that each of the three zones had a distinct pattern of psychological processes associated with it. Moreover, we also found appreciable fine-grained variation in

psychological functions between sub-regions within each zone. Collectively, our results provide insight into the functional topography of MFC at multiple anatomical scales and suggest that previous studies may have overstated the case for the convergence of different processes in MFC.

Materials & Methods

We analyzed the Neurosynth database (Yarkoni et al., 2011), 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. Scikit-learn (Pedregosa et al., 2011), a Python module, was used for all machine learning analyses in this study. Code and tutorials to replicate this analysis on any given region are available as part of the Neurosynth code base (https://github.com/neurosynth/neurosynth).

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). We then calculated the correlation between each MFC voxel with the rest of the brain across all studies in the Neurosynth dataset. 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 between every voxel in the MFC ROI with each PCA

component, resulting in a 15259 x 100 feature matrix (where each row is an MFC voxel, and each column is a loading on a single PCA component). We applied k-means clustering to this matrix, as this algorithm is computationally efficient, widely used, and shows high goodness of fit and reproducibility (Thirion et al., 2014). 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 (Poldrack & Yarkoni 2016). 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 (Wager et al., 2008) in order to estimate the uncertainty around scores. 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

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 directly contrast co-activation patterns between zones and sub-regions within each zone by performing a meta-analysis that contrasted studies that uniquely activated each ROI to studies that activated other parcels in the same analysis (e.g. studies that activated anterior MFC vs studies that activated middle and 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 two-way chi-square test (see (Yarkoni et al., 2011) for more details). Next, we thresholded significant voxels using False Discovery Rate correction at $p < 0.01$ and binarized the resulting maps for display. We created 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'), as well as 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 (LDA) topic-modeling. This procedure was identical to that used in a previous study (Poldrack et al., 2012b), 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. See Table 1 for a list of topics most associated with MFC.

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 (i) we have previously had success applying this algorithm to Neurosynth data (Yarkoni et al., 2011); (iii) these algorithms perform well on many types of data (Androutsopoulos et al., 2000), (iii) they require almost no tuning of parameters to achieve a high level of performance; and (iv) they produce highly interpretable solutions, in contrast to many other machine learning approaches (e.g., support vector machines or decision tree forests).

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 mean score across all folds as the final measure of performance. We scored our models using the area under the curve of 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 (Jeni et al., 2013). This was important because each region varied in the ratio of studies that activated it to the studies that did not. For all regions, we were able to predict activity at moderately accurate levels, averaging an AUC-ROC of 0.63 (range: 0.609 – 0.663) for the three zone parcellation and AUC-ROC of 0.6 for the nine-region parcellation (range: 0.567 – 0.643).

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 reported associations significant at the $p<0.001$ threshold.

Results

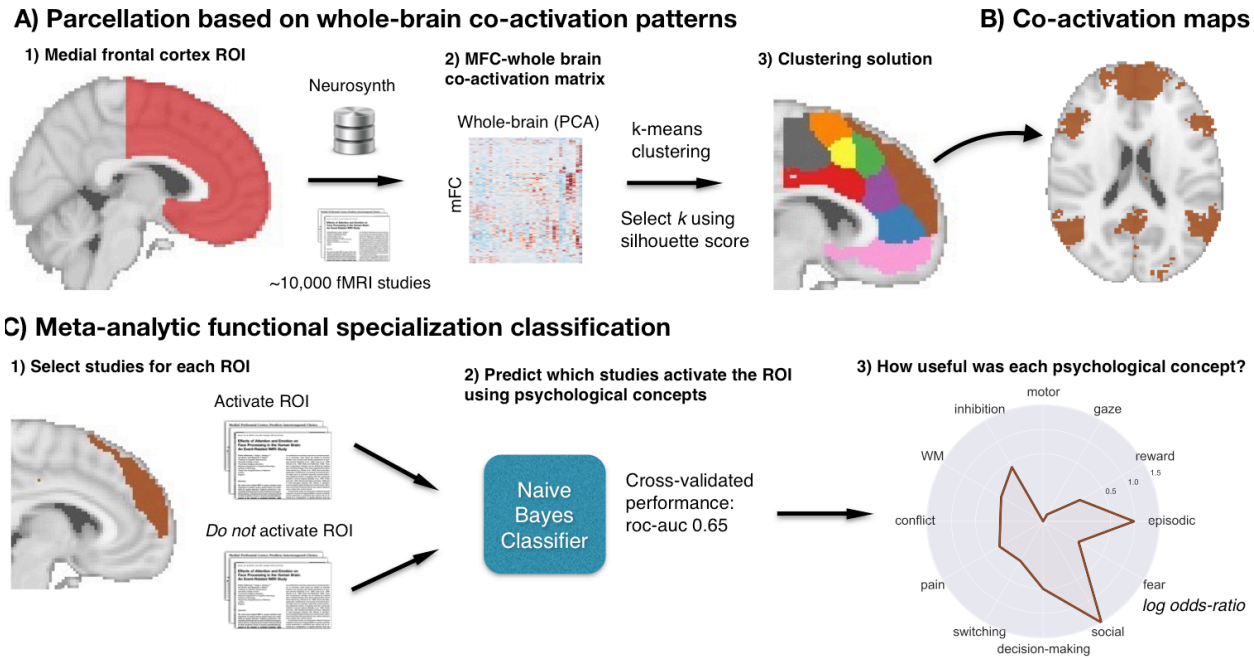

Figure 1. Methods overview. A) Whole brain co-activation of MFC voxels was calculated and k-means clustering was applied resulting in spatially distinct clusters. B) For each cluster, thresholded whole-brain co-activation maps were generated. C) We functionally characterized each cluster by determining 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 (Toro et al., 2008; Smith et al., 2009; Chang et al., 2013), an approach that exploits the likelihood of a voxel co-activating with another voxel across studies in the meta-analytic database (Figure 2). 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, and absolute

maxima with 12 clusters (Figure 3). We focus on the 3- and 9- cluster solutions as they provide insight into the functional topography of MFC at two different scales. Although the 12-cluster solution results in a marginally better silhouette score, this comes at the cost of additional complexity.

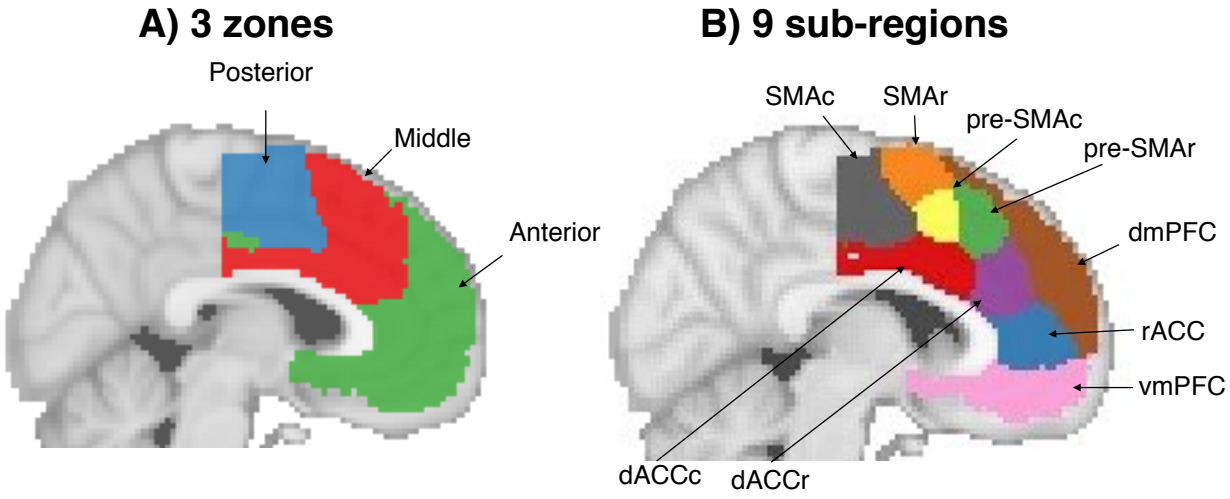

Figure 2. Co-activation-based clustering of MFC at two levels of granularity. A) Three broad functional zones along a rostral-caudal axis. B) Nine-subregions hierarchically organized within the zones. SMA: supplementary motor area; dACC: dorsal anterior cingulate cortex; rACC: rostral anterior cingulate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

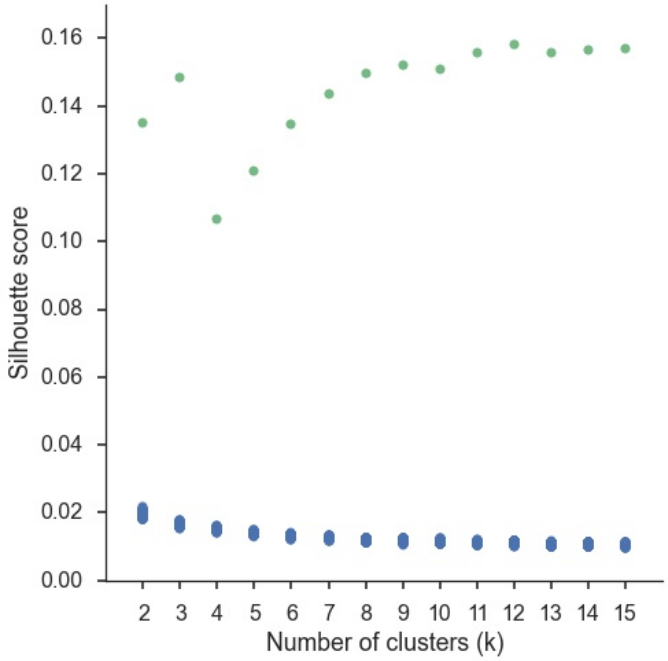

Figure 3. Silhouette scores of real (green) and permuted (blue) clustering solutions. Clustering was performed on permuted data 500 times for each k to compute a null distribution. We z-scored real clustering scores and determined they were all significantly greater than chance ($p<.0001$). Silhouette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

At the coarsest level, MFC divided into three broad bilateral zones organized along the rostral-caudal axis. 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 (Vogt, 2005); and 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 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 cytoarchitechtonic findings. Within the posterior zone, we identified two clusters consistent with rostral and caudal SMA (Vorobiev and Luppino, 1998). Within the middle functional zone, we identified two clusters dorsal to the cingulate sulcus consistent with pre-SMA (Picard and Strick, 1996) and two ventral clusters consistent caudal and rostral dACC (Vogt, 2005). Within the anterior zone, we identified a rostral ACC cluster that delineated from ventral mPFC (vmPFC) (Vogt, 2005) 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 exclusively using a functional co-activation based approach converged with many distinctions previously drawn on the basis of anatomical criteria.

However, as these parcellations do not provide direct insight into the functions of the resulting clusters, we applied two approaches to better understand the functional nature of the zones and sub-regions identified. First, we determined which other brain regions co-activate with each zone and sub-region, in order to reveal the functional networks of each region. Second, we probed the semantic metadata from Neurosynth to determine which psychological concepts predict the activation of each of these zones and subregions.

Meta-analytic co-activation profiles

We directly contrasted co-activation patterns of the three functional zones---i.e., we sought to identify voxels that co-activated to a stronger degree with each zone than with the other two (Figure 4A). The posterior zone showed greater 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 motoric function. The middle zone co-activated with 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 to a greater extent with default network regions such as angular gyrus, hippocampus and posterior cingulate cortex (PCC) (Andrews-Hanna, 2012). The anterior zone also showed greater co-activation with subcortical regions important for affect-- the amygdala and ventral striatum (VS).

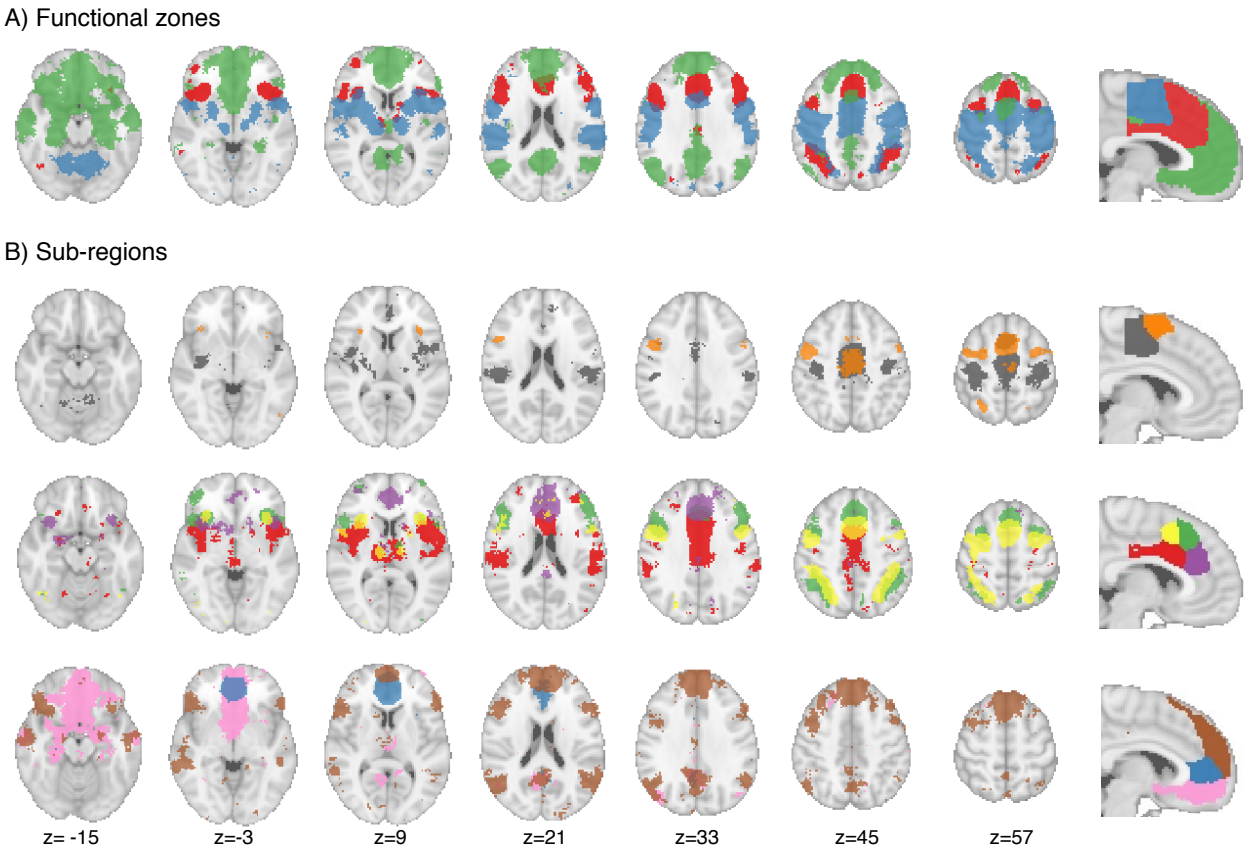

Figure 4. Functional co-activation networks of MFC zones (A) and sub-regions within each zone (B). Colored voxels indicate significantly greater co-activation with the seed region of the same

color (at right) than other regions 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 a false discovery rate (FDR) of $q = 0.01$.

To understand the differences in co-activation found within each zone, we directly contrasted co-activation patterns of each zone's sub-regions (Figure 4B). 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 (Nelson et al., 2010b; Chang et al., 2013). Within the middle zone, we found that all four sub-regions strongly co-activated with various aspects of the insula. However, caudal dACC was more strongly co-activated with pIns as well as SII and the brain stem—important regions for pain processing (Vogt, 2005; Wager et al., 2013). In contrast, rostral dACC co-activated more strongly with ventral aIns as well as lateral OFC—regions previously associated with chemosensory processing (Rolls et al., 1990; Yaxley et al., 1990) and reward-driven learning (Schoenbaum and Roesch, 2005). 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 in cognitive control at different levels of abstraction.

Within the anterior zone, rACC did not show many co-activation differences from its neighbors. Surprisingly, both dmPFC and vmPFC showed greater co-activation with PCC – 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) (Carter and Huettel, 2013) and the superior temporal sulcus (STS) (Zilbovicius et al., 2006), 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 identified are involved with distinct functional networks, and suggest that there are likely broad functional differences across MFC zones, accompanied by fine-grained differences within each subregion.

Meta-analytic functional specialization

To test if MFC zones and sub-regions exhibited distinct patterns of functional specialization, we used a data-driven approach that surveyed a broad range of psychological states to identify those maximally predictive of activation in each MFC region. For each cluster, we trained a multivariate classifier to predict which studies activated the cluster using a set of 35 psychological concepts derived by applying a standard topic modeling approach to the text of articles in the database (Poldrack et al., 2012a) (Table 1). 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 (Figure 5). 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 implicated in negative affect—pain and fear – as well as decision-making. Consistent with its distinct pattern of co-activation, the anterior zone showed a robust shift away from goal-

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

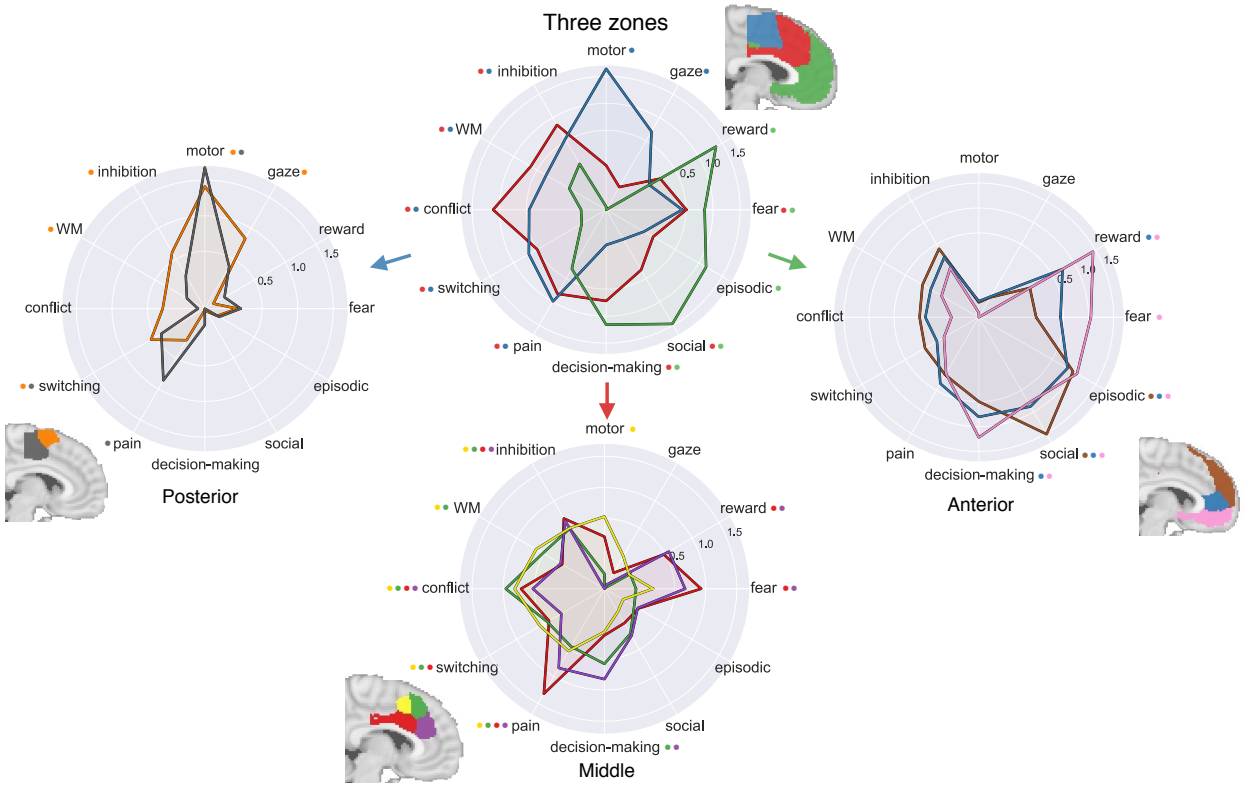

Figure 5. Functional specialization profile of MFC clusters. Each cluster was profiled to determine which psychological concepts best predicted its activation. Top) Each of the three functional zones we identified showed distinct functional profiles with broad shifts across cognitive domains Bottom) Within each zone, sub-regions showed fine-grained shifts in functional profile. Strength of associations is measured in log-odds ratio, and permutation-based significance ($p<0.001$) 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 patterns of psychological function, similar to the fine-grained variations in co-activation previously observed for each subregion. In the posterior zone, activity in both clusters was similarly predicted by motor function and switching. However, only caudal SMA was significantly 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 predicted by aspects of cognitive control (i.e. 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 found that only activity in caudal pre-SMA was significantly predicted by motor function, while activity in rostral pre-SMA and dACC was significantly predicted by decision-making.

In the anterior zone, activity across all three sub-regions was significantly predicted by episodic memory and social processing; however, the association with social processing was maximal for dmPFC, consistent with a previous meta-analysis (Denny et al., 2012). In contrast, the reverse was true for reward and decision-making: only activity in rACC and vmPFC was significantly predicted 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.

Topic name	Highest loading words
gaze	eye gaze movements eyes visual saccades saccade target fixation direction
decision-making	decision choice risk decisions choices uncertainty outcomes risky taking outcome
episodic	memory events imagery autobiographical retrieval episodic memories future mental semantic
motor	motor movement movements sensorimotor primary finger control imagery tasks force
social	social empathy moral person judgments mentalizing mental theory people mind
reward	reward anticipation monetary responses rewards motivation motivational loss incentive punishment
switching	cues target trials cue switching stimulus targets preparation switch selection
conflict	conflict interference control incongruent trials stroop congruent cognitive behavioral rt
inhibition	inhibition control inhibitory stop motor trials nogo cognitive suppression aggression
fear	fear anxiety threat responses conditioning cs extinction autonomic conditioned arousal
working memory	memory performance cognitive wm tasks verbal load executive test maintenance
pain	pain painful stimulation somatosensory intensity noxious heat nociceptive placebo chronic

Table 1. Topics most strongly associated with MFC regions used in Figure 5. Ten strongest loading words for each topic are listed, in descending order of association strength.

Discussion

In the current study, we identified and functionally characterized regions of the medial frontal cortex by applying a data-driven approach to a large-scale database of ~10,000 fMRI studies. The present results extend on previous organizational schemes derived from more static measures of neural organization, such as cytoarchtechtonics, DTI, and rs-fMRI, by deriving functional units based on co-activation and then directing linking them to psychological function across a diverse range of psychological processes. At a coarse level, we identified three broad zones arranged along the rostra-caudal axis with distinct patterns of whole-brain co-activation. Multivariate analyses aimed at determining the psychological concepts most highly associated with each region revealed similarly distinct functional signatures for each of these zones. We further fractioned each zone into 2-4 sub-regions that varied more subtly in both whole brain co-activation patterns and psychological function.

Posterior zone

The posterior MFC zone identified by our method spanned regions previously associated with motoric function--such as SMA and caudal cingulate zone (CCZ)-- and delineated from pre-SMA in a manner consistent with cytoarchitectonics (Vorobiev and Luppino, 1998; Vogt, 2005) and rs-fMRI (Kim et al., 2010). This zone was primarily associated with motor function and co-activated with key motor regions such as primary motor cortex and thalamus. Our results suggest that posterior MFC can be further functionally fractionated into caudal and rostral sub-regions. Caudal SMA—which includes CCZ— showed a greater association with pain processing and greater co-activation with key pain regions such as SII and thalamus. Given that pain signals often indicate the need for motor action to avoid damage to the organism, caudal SMA may be specialized in initiating movements in response to pain. In contrast, in addition to motor function, rostral SMA was implicated in cognitive control and co-activated with regions important for goal-directed cognition such as DLPFC and aIns. These results are consistent with the hypothesis that the supplementary eye fields (located in our rostral SMA cluster) are important for high-level control of eye movements (Corbetta et al., 1998; Everling and Munoz, 2000). While rostral SMA is unlikely to be involved in the resolution of conflict or direct maintenance of items in WM – usually considered the providence of DLPFC— direct cortico-spinal connections in this region (Luppino, 1993) suggest it is well situated to modify motor action to support goal-directed cognition.

Middle zone

The middle MFC zone in our study was associated with several aspects of cognitive control and negative affect. While these findings seem consistent with hypotheses suggesting

that "dorsal ACC" is important for the integration of negative affect into cognitive control (Shackman et al., 2011), our findings suggest a substantial functional-anatomical specificity not accounted by such theories. Although all four middle MFC sub-regions were significantly associated with aspects of cognitive control, and co-activated with related sub-regions (e.g. DLPFC and aIns), the two pre-SMA subregions showed greater associations with cognitive control processes—in particular WM— and co-activated more strongly with regions in the so-called 'fronto-parietal control network'. In contrast, dACC sub-regions were more strongly associated with affect, with caudal dACC showing a stronger affinity for pain, while rostral dACC showed a greater association with decision-making.

Our results are in contrast with accounts of cognitive control that hypothesize dACC to be the MFC region primarily responsible for conflict processing. Instead, our results support an alternate hypothesis in which negative affective signals that indicate conflict may be initially processed in dACC and are integrated in pre-SMA with high-level goals –likely represented in DLPFC. Our findings are consistent with previous single-cell recording in macaques that primarily show conflict related activity in cells in pre-SMA and not dACC (Nakamura and Roesch, 2005; Cole et al., 2009). Moreover, the significant association of rostral pre-SMA and rostral dACC with decision-making (and co-activation with lateral OFC) lend support to theories suggesting that control of responses within the context of current goals depends on dopaminergic learning signals as to avoid future negative outcomes (Brown and Braver, 2005).

Anterior zone

Our results for anterior MFC yielded a functional signature distinct from the rest of MFC with strong associations with affect, decision-making, social cognition, and episodic memory.

This was accompanied by co-activation with regions of the default network, such as PCC, hippocampus, and sub-cortical regions such as amygdala and VS. Yet as with the other two main zones, our results suggest that anterior MFC zone 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 (Mitchell et al., 2006) and it has strong co-activation with TPJ, a region hypothesized to be important for mentalizing (Baumgartner et al., 2012; Denny et al., 2012). Rostral ACC showed a relatively less specific functional pattern, showing moderate associations with both affective processes and decision-making, perhaps consistent with descriptions of the existence of a default network 'hub' region in mPFC (Andrews Hanna et al., 2010; van den Heuvel and Sporns, 2013). Finally, vmPFC was primarily associated with relatively low-level affective processes, such as reward and fear, consistent with its robust sub-cortical co-activation. Although some have characterized vmPFC as a 'valuation' system (Lebreton et al., 2009), our results suggest that vmPFC is equally important for affective processes traditionally associated with the amygdala, such as fear. vmPFC may play a more general role of incorporating into the cortex various kinds of sub-cortical affective signals, while more dorsal regions may integrate these signals with the rest of the default network (Roy et al., 2012).

Despite the additional functional-anatomical specialization that we observed within MFC, it is notable that no region in MFC is selectively activated by a single psychological concept. At least two distinct concepts significantly predict activation in each cluster, even at the relatively stringent permuted threshold of $p<0.001$. Thus, while each region we identified showed a distinct functional signature, our results suggest a complex many-to-many mapping between functionally separable brain regions and cognitive processes. This stands in contrast with recent arguments of

functional selectivity in MFC, such as dACC being selective to pain (Lieberman and Eisenberger, in press).

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 regions. Although this topic model provides a substantial improvement over term based meta-analysis (Poldrack et al., 2012a), these topics are still based purely on the frequency with which terms appear in the abstracts describing fMRI articles, and are not able to capture more complex semantic structures. Second, the quality of activation data in Neurosynth is inherently limited due to its automatically generated nature. However, previous validation analyses have shown that these limitations are unlikely to contribute systematic biases to the data (Yarkoni et al., 2011), and the large-scale nature of our approach (N= 9,721) ameliorates these concerns. 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 (Paus, 2001; Cole et al., 2009). While only advances in MR technology will improve spatial resolution, the open sharing of low-level fMRI data will enable large-scale meta-analyses with subject-specific anatomical registration (Gorgolewski et al., 2015).

The present results provide a unique viewpoint into the functional organization of medial frontal cortex by leveraging the wealth of experimental fMRI studies linking psychological functions to structure. Although the anatomical organization of this area has been extensively

studied using a variety of methods—such as cytoarchitechtonics, DTI and rs-fMRI—such approaches lack the ability to directly link hypothesized sub-regions to psychological function. Here we focus on identifying regions that show differential co-activation and functional patterns across the variety of psychological states elicited by the tasks in the Neurosynth database. Importantly, as each of these approaches attempts to optimize different criteria in search for organizational units, we should not necessarily expect these different parcellations to perfectly align. Yet in our approach they did so to a very substantial degree. Nonetheless, future studies that formally integrate across modalities, such as meta-analytic co-activation, cytoarchtechtonics, DTI, and rs-fMRI, may provide additional insights to the organization of medial frontal cortex, as well as the rest of the brain.

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