Classification: Biological Sciences; Neuroscience

Title: Functional specialization and complexity of human medial frontal cortex

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**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 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 medial frontal cortex 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 multi-variety 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 but robust shifts in functional specialization within each zone, suggesting that existing accounts of convergence in MFC may be overstated.

**Significance Statement**

The medial frontal cortex is a cortical area that has been associated with many psychological processes using functional MRI. This diversity, 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.

**Significance Statement.** 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.

**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 (1-5), while nearby dorsal anterior cingulate cortex (ACC) has been implicated in various aspects of cognitive control, such as conflict (6-8) and error processing (9-11), and is thought to be important region for pain processing (12-15). Further anterior, medial prefrontal cortex (mPFC) and subgenual ACC have been shown to be important for a variety of affective processes, including emotion (16-18), autonomic function (19), and valuation (20-22). Furthermore, portions of mPFC have also been associated with a variety of stimulus-independent internally oriented processes, such as mentalizing (23, 24) and autobiographical memory (25, 26).

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. (16, 27) or restrict themselves to a small region of interest (e.g. (28). 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 (29). This concern is particularly acute in the case of MFC regions pre-SMA and dACC, suggesting low selectivity to a given domain (30, 31).

Here we attempt systematically create a comprehensive functional-anatomical mapping of medial frontal cortex using Neurosynth, a diverse large-scale functional neuroimaging database of over 10,000 studies (31). 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 (32-34), 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**

## 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:2008iu}{Smith:2009bh}{Chang:2013kx}, 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. We assessed the validity of these solutions 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).

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 {Vogt:2005gm} 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). Generally, the sub-regions we identified were consistent with prior cytoarchitechtonic work. Within the posterior zone, we identified two clusters consistent with rostral and caudal SMA {Vorobiev:1998wk}. Within the middle functional zone, we identified two clusters dorsal to the cingulate sulcus consistent with pre-SMA {Picard:1996ea}{Rizzolatti:1996ku} and two ventral clusters consistent caudal and rostral dACC (also known as midcingulate cortex) {Vogt:2005gm}. Within the anterior zone, we identified a rostral ACC cluster that delineated from ventral medial prefrontal cortex (vmPFC) {Vogt:2005gm} and 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 whole-brain co-activation patterns of the three functional zones, controlling for co-activation in other zones (Fig. 3). The posterior zone showed bilateral co-activation with lateral motor and parietal cortices, 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 superior parietal cortex (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) (38). The anterior zone showed strong co-activation with subcortical regions important for affect-- the amygdala and ventral striatum (VS).

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 the aIns— regions associated with goal-directed cognition (37, 40).

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—crucial regions for pain processing (12, 15, 43). In contrast, rostral dACC co-activated more strongly with ventral aIns, as well as lateral OFC—regions previously associated with chemosensory processing {Yaxley:1990kb}{Rolls:1990kb} and reward-driven learning (46). In contrast, both caudal and rostral pre-SMA were strongly associated with dorsal aIns, in addition to regions in the frontoparietal control network (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 (48).

Within the anterior zone, we rACC did not show many co-activation differences from its neighbors, suggesting rACC may be primarily involved with local processing. In fact, 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) (49) and superior temporal sulcus (STS) (50), 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 broad functional differences across MFC zones, and more fine-grained differences between sub-regions.

## 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 their activation. For each cluster, we trained a multivariate classifier to predict which studies activated the given cluster using a set of 34 psychological concepts derived by applying a standard topic modeling approach to the text of articles in the database (Poldrack et al., 2012) (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.

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 (24). 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 cognitive 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 cognitive 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 cognitive 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. We chose the next concept to add by trying all remaining concepts and adding the one that improved performance the most. We repeated this processes 1000 times for each region to account for sampling error (e.g. bootstrapping) 5A). Not surprisingly, activation of all regions was better predicted as the number of cognitive functions in the model increased, reaching peak performance on average with 23.8 functions (receiver operating characteristic area under the curve (ROC-AUC) of 0.62). Eventually, accuracy decreased when too many uninformative features were added to the model.

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 cognitive 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 cognitive 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. On the basis of meta-analytic co-activation with the rest of the brain, we identified three distinct functional zones along a rostra-caudal axis. We discovered that MFC further fractionated into nine subregions which spatially corresponded with the three zones and were anatomically consistent with cytoarchitechtonic studies (Vogt et al., 2005). Next, we used machine-learning classification to identify the cognitive concepts which best predicted activation for each of these MFC parcels, revealing broad distinctions in function across the three functional zones and finer-grained shifts in specialization between sub-regions within each zone. Finally, we quantified the complexity of function found in each of these regions, and found that regions previously hypothesized to show high diversity, such as pre-SMA and dACC, only show moderate amounts of functional complexity. Below, we discuss the results for each functional zone separately, and conclude with limitations and future directions of large-scale meta-analysis.

Posterior functional zone

The posterior functional zone of MFC was robustly associated with the relatively specific role of motor function. This posterior zone spanned portions of MFC previously associated with motoric function, such as SMA, and delineated from more anterior regions thought to support more high-level cognitive processes, such as pre-SMA, in a manner consistent with cytoarchitechtonic (Vogt et al., 2005, Vorobiev et al., 1998; Luppino, 1993), tractography (Klein et al. 2007) and resting-state functional connectivity (Kim et al., 2010). The whole-brain co-activation of this zone supported a strong role in motoric function, primarily co-activating with lateral motor cortices and sub-cortical regions such as the thalamus. The functional characterization of this zone was consistent with this co-activation pattern as activation in this zone was primarily predicted by general motor function and eye gaze, and to a lesser extent pain processing.

Posterior MFC further fractionated into a caudal and rostral subdivisions consistent with cytoarchtechtonic evidence suggesting SMA is composed of at least two functionally separable regions (Luppino, 1993; Vorobiev et al., 1998). While a strong association with motoric function primarily characterized both sub-regions, our results suggest that caudal SMA is also involved in pain processing while rostral SMA is more involved with goal-directed cognition and inhibitory processes. In particular, caudal SMA showed stronger co-activation with the thalamus, SII and dorsal somatosensory cortex—regions previously identified to be important for pain (15). Consistent with this pattern, activity in caudal SMA was also predicted by pain processing. Moreover, caudal SMA showed relatively low functional complexity, suggesting this region is fairly specifically involved with motor and pain processing. Given that pain signals often indicate that motor action must be taken to avoid inflicting damage to an organism, this region may be particularly specialized in taking quick action in response to harmful, painful stimuli.

In contrast, our results suggested rostral SMA is likely to be important for goal-directed motor function. Rostral SMA co-activated with posterior lateral prefrontal cortex and anterior Insula—regions hypothesized to be important for effortful, controlled action. Consistent with these findings, rostral SMA was associated with eye gaze function and several aspects of cognitive control, most notably inhibition. These results are consistent with long-standing notion that the supplementary eye fields (SEF), which are located within our rostral SMA parcel, are important for high-level control of eye movements, in tasks such as anti-saccade (51, 52). Thus, while rostral SMA is unlikely to be involved in the resolution of cognitive control processes, the known direct cortico-spinal connections possessed by this region suggest it is well situated to send direct inhibitory motor signals. Moreover, this region may be important for lower-level aspects of cognitive control such as stimulus-response mapping.

Middle functional zone

The middle functional zone of MFC—encompassing pre-SMA and dACC—was characterized by its involvement with a variety of cognitive control processes and affective processes. 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 (Shackman et al., 2011). However, upon closer inspection, our results suggests that there is substantial functional-anatomical specificity that has thus far been underappreciated due to this region’s very high activation rate (Yarkoni et al., 2011). These distinctions are only appreciable when this broad zone is divided into smaller functional regions and analytical methods that appropriately control for base rate of activation are used to characterize their functions.

In particular, we identified four sub-regions with dissociable patterns of co-activation within the middle MFC zone: caudal and rostral pre-SMA and caudal and rostral dACC. These subdivisions are consistent with extensive cytoarchitectonic work in monkeys and humans (Vogt et al., 2005) indicating that caudal dACC and rostral dACC (also known as anterior and posterior midcingulate cortex) show distinct cellular organization and demarcate from pre-SMA along the cingulate sulcus. Our functional specialization analysis indicates that although all four regions co-activate with regions important for goal-driven cognition, such as dorso-anterior insula, the two pre-SMA subregions show much stronger associations with most aspects cognitive control-- in particular working memory. These functional differences are supported by the fact that both pre-SMA clusters showed greater co-activation with regions in the frontoparietal control network (e.g. DLPFC, and SPC). In contrast, activity in the dACC clusters was much more strongly associated with affective processes-- such as fear, reward and pain. The present results suggest that existing accounts of integration between negative affect and cognitive control in MFC may be overstated.

The dissociation between pre-SMA and dACC found in our data suggests that existing models of cognitive control underspecify the functional topography this middle zone of MFC and may misattribute functions to dACC, when in fact they are likely supported by pre-SMA proper. Some influential theories of cognitive motoric control consider dACC to be the region primarily responsible for conflict processing (Botvnick et al., 2001, 2004)(11). However, concerns have previously been raised that macaques primarily show conflict related activity in pre-SMA and not dACC, unlike humans (Nakamura, Roesch & Olson, 2005; Rushworth, Walton, Kennerley, Bannerman et al., 2004; Cole, Yeung, Freiwald, & Botvinick, 2009). Our results suggest that human conflict-related activity, in addition to other cognitive control processes, is also most associated pre-SMA proper, not dACC. Thus, a possible hypothesis is that signals that indicate possible conflict may enter cortex and be initially processed in dACC, but these signals are only likely to be integrated with goal-directed processing in pre-SMA.

Finally, we also found evidence that the two sub-regions of dACC proper specialized in different types of affective processes. Caudal dACC was much more strong associated with pain than any other regions, consistent with its strong co-activated with the thalamus—an important region in pain perception (Aziz et al., 2006; Wager et al., 2013). In contrast, rostral dACC was more strongly associated with decision-making and reward, consistent with its stronger co-activation with the nucleus accumbens and lpOFC—regions important for reward processing (46, 47). Interestingly, rostral pre-SMA was also associated with decision-making and co-activated with lpOFC, consistent with theories suggesting that conflict is better described as the process of learning how to avoid future negative outcomes. Our results suggest that rostral pre-SMA and dACC are more important for interacting with other brain-system important for learning, whereas caudal pre-SMA and dACC may be more important for integrating negative affective signals into conflict processing.

Anterior functional zone

Finally, at the most anterior portions of MFC, we identified a functional zone composed of three subregions: vmPFC, rACC and dmPFC. This zone showed a fairly distinct pattern of functional specialization, showing very low associations with motor and executive functions and strong associations with affective processes, decision-making, and social cognition. This distinct pattern of functional was accompanied by a distinct pattern of whole-brain co-activation, primarily co-activating with regions of the default network, such as posterior cingulate cortex (PCC), the precuneus, the hippocampus and sub-cortical regions such as the amygdala and nucleus accumbens. These results are consistent with extensive evidence suggesting medial prefrontal cortex is a key portion of the ‘default network’ (38) that is relatively removed from the processing of external stimuli and actions.

Anterior MFC broke down further into three subregions: a dorsal parcel (dmPFC), a middle cluster primarily situated in rostral anterior cingulate cortex (rACC), and a ventral cluster (vmPFC) encompassing medial OFC and subgenual ACC. The three regions were similarly associated with both emotion and episodic memory, suggesting these two processes rely on the entire medial prefrontal cortex. However, dmPFC was much more strongly associated with social processing, consistent with several studies linking dmPFC to social perception and self-referential thought (53, 54). Moreover, dmPFC showed strong co-activation with TPJ, a region thought to also be important for mentalizing (23, 24). Importantly, dmPFC showed very low association with reward processing, suggesting that higher-level mentalizing processes occur separately from low-level affective processing.

Ventral to dmPFC, rACC showed a less specific functional pattern, showing moderating associations with a variety of process, including low-level affective processes such as fear, reward and emotion as well as higher-level processes such as decision-making, episodic memory. This was consistent with the high functional complexity we observed in this region—a model with many cognitive concepts was required to accurately predict activity in this region. These findings are consistent with descriptions of the existence of a default network ‘hub’ region in mPFC (55, 56). 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. However, we also found that rACC showed lower co-activation with other key regions of the default network, such as PCC, compared to vmPFC and dmPFC. Thus, more work is needed to determine if rACC is truly a global default network hub.

Finally our results suggest that vmPFC, the most ventral region in MFC, is primarily associated processes directly related to affective signals. Activity in vmPFC was very strongly predicted by affective processes, such as reward and fear. This function is consistent with its strong co-activation with subcortical regions known to be important for these processes, such as the nucleus accumbens (57) and amygdala (58, 59) , respectively. However, vmPFC was also associated with higher-level cognitive processes that are known to depend on these affective signals, such as decision-making (60, 61) and memory (62, 63). Importantly, although some have characterized vmPFC as being a ‘valuation’ system (64), these results suggest that this region is equally important for processes more closely related with the amygdala and related negative emotions. Our results suggest that vmPFC may more generally be involved in the integration of various affective signals into cortex, while more dorsal regions, such as rACC may be important for integrating or contextualizing these signals into higher-level processes (65).

Limitations

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 discriminating the activity of certain regions. Although this topic model provides a substantial improvement over term based meta-analysis (66), 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 such as sentences which may denote more fine-grained differences in function. Nonetheless, topic-modeling based ontologies are surprisingly consistent with neuroscientific knowledge suggesting that the current approach provides a useful, if coarse, functional-anatomical mapping. 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 instead primarily reduce the overall spatial fidelity of the database (Yarkoni et al., 2011). Thus, the large 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 both the activation extraction and semantic annotation may further 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 dorsal ACC, where BA 32’ lies only a few millimeters dorsal of BA 24, and shows particularly large anatomical variation across humans (45, 67). While only advances in radiology will improve the spatial resolution of fMRI, the open sharing of full fMRI data may improve this situation by enabling research to perform large-scale meta-analysis with higher quality data, including perhaps individualize registration to anatomy on a subject-by-subject basis. The benfit 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. We suggest that the functional-anatomical mappings and modest classification performance we are able to achieve with this relatively noisy data suggest that applying similar data-driven methods to higher quality data will result in precise estimates of functional specialization in the future.

# Conclusion

In the present study, 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. The most posterior zone is distinctly involved motor function, the middle zone is important for both negative affect and cognitive control processes while anterior MFC likely integrates affective signals into higher-level internally oriented processes. 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 (neurosynth.org; Yarkoni et al., 2011), a repository of 9,721 fMRI studies and over 350,000 activations. Each observation in the database 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 were smoothed using a 6mm Gaussian kernel.

### Medial frontal cortex co-activation clustering

To find separable regions in medial frontal cortex, we clustered individual voxels inside of a medial frontal cortex mask based on their coactivation with voxels in the rest of the brain. First, we defined a medial frontal cortex volume of interest mask in standard Montreal Neurological Institute (MNI) to select the appropriate voxels. We used FSLView to create a mask of voxels with greater than 30% probability of being grey matter according to the Harvard-Oxford anatomical atlas. Next, we excluded all voxels that were more than 10mm from the midline of the brain in the X dimension, as a way to exclude grey matter voxels on the lateral surface of the brain. We also excluded voxels that were posterior to central sulcus (Y < -22) and voxels that were ventral to vmPFC (Z < -32), such as temporal cortices, resulting in a somewhat liberal mask of medial frontal cortex. Next, we took this somewhat liberal mask and excluded voxels that showed very low activation in the database (less than 80 studies per voxel).

Next, we calculated the correlation between each medial frontal cortex voxel with the rest of the brain across studies. As this would result in a very large matrix which would be computationally difficult to cluster, we first reduced the dimensionality of the rest of the brain using principal components analysis. We applied principal component analysis using randomized singular value decomposition 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, for each voxel in the MFC mask, we computed the correlation distance of every voxel in MFC with each PCA component defined as 1 - \frac{(u - \bar{u}) \cdot (v - \bar{v})}         {{||(u - \bar{u})||}_2 {||(v - \bar{v})||}_2}, where *u* is a MFC voxels and *v* is a whole-brain PCA component, resulting in a MFC distance matrix.

We used k-means clustering to group MFC voxels, as this algorithm is computationally efficient, commonly used, and shows high goodness of fit and reproducibility (Thirion, Varoquaux, Dohmatob, & Poline, 2014). We then used scit-kit learn’s implementation of k-means clustering to the MFC distance matrix using the k-means++ initialization procedure. The k-means algorithm was run 10 times on different centroid seeds and the best output of these consecutive runs was selected in terms of inertia to avoid local minima.

Because structure-to-function mappings can be identified at multiple scales, with potentially different (but equally valid) results, we conducted our analyses at multiple levels of spatial resolution. We parcellated the MFC into 2 through 15 regions. Identifying the ‘correct’ number of clusters is arguably an intractable problem, 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 (for discussion, see Poldrack and Yarkoni, in press). 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. Solutions that minimized the average distance between voxels within each cluster received a greater score. 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. Higher scores indicate tighter clustering of the data.

However, because it is unclear what should be considered a significant silhouette score, we used a permutation procedure previously employed by our group (68) to infer if a given clustering solution was warranted. For each possible solution between 2 and 15 clusters, we permuted the data matrix indicating which voxels were activated by which studies, generating a new permuted data set with no relationship between voxels. We then re-applied the clustering algorithm, and re-calculated the silhouette score. This was repeated 1000 times for each number of clusters, resulting in a null-hypothesis distribution of silhouette scores for each *k*. Estimating the null distribution of silhouette scores allowed us to calculate a Z-score for the silhouette score based on our observed data clustering solutions. Figure S1 shows the silhouette score for each clustering solution and below it the silhouette scores of the null-distribution. All clustering solutions were very significant (all z-scores were greater than XX), and the null-distribution stayed relatively stationary as the number of clusters increased.

Given the high statistical significance of all clustering solutions, we qualitatively assessed the silhouette scores of our real clustering solutions. Silhouette scores reached a local maxima with three clusters, suggesting that this simple organizational scheme explained a surprisingly high amount of the data. Silhouette scores then dipped and reached another local maxima using nine clusters. Beyond nine clusters, silhouette scores marginally increased, but in our estimation not sufficiently so to warrant the increase in complexity in the clustering solutions. Thus, we selected three and nine regions as the most useful clustering solutions, but note that solutions with 12 and 14 regions also showed high silhouette scores, and sensible solutions, thus we include them as a supplement (Fig. SII).

### Co-activation profiles of MFC clusters

To calculate co-activation profiles of each cluster, we performed a whole-brain meta-analysis of studies that activated each MFC parcel. This analysis resulted in a whole-brain map indicated the extent to which voxels activated in the studies that activated each MFC parcel. We selected studies that activated at least 25% of voxels in a given parcel and then performed a forward-inference meta-analysis. See the section below on meta-analysis for more details on the procedure.

### Topic modeling

Although the term-based meta-analysis maps in Neurosynth closely resemble the results of manual meta-analyses of the same concepts (e.g. Yarkoni et al., 2011; Bartra, McGuire & Kable 2013), 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 dilemma, 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 paper (Poldrack, Mumford, Schonberg, Kalar, Barman, & Yarkoni, 2012), 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 occurring in the abstracts of studies in the Neurosynth database. Each resulting 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. Likewise, as each topic maps onto individual studies to a varying extent, the topic model facilitates the categorization of the cognitive phenomena studied across fMRI studies; for example, a study that maps highly onto a topic described by the words 'control, inhibition, conflict’ is likely to be examining cognitive control. Out of the 60 generated topics, 25 represented non-cognitive semantic topics, such as the nature of the subject population (e.g. gender, special populations) and methods (e.g., words such as “images”, “voxels”. In order to focus on the cognitive predictors of brain activity, we identified these topics and excluded them from all analyses (see Appendix for a list of included and excluded topics).

### Meta-analytic functional specialization

For each cluster, we built a linear model to predict whether activity in that region would be reported by an fMRI study based on the semantic content of the words used to describe the focus of that fMRI study. This procedure allowed us to generate functional profiles that describe which cognitive functions best predicted the activity of each region, and how well fMRI activity can be explained by the cognitive theory present in the body of fMRI studies at the meta-analytic level. Below, we describe each step of our approach.

We generated functional profiles of MFC regions by determining which cognitive functions 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 absolutely no voxels in the parcel. For each parcel, we trained a naive Bayes classifier to discriminate these two sets of studies based on the semantic content of the studies herein. We chose naive Bayes because we have previously had success applying this algorithm to Neurosynth data in the past (Yarkoni et al., 2011), and has been shown to perform well on many types of data (69). In addition, naive Bayes classifiers require almost no tuning of parameters to achieve a high level of performance, decreasing the likelihood of an overfit of the model to the data.

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 employed 4-fold cross validation to test the generalization of our models. Models were fitted on 3/4ths of studies and tested on the remaining studies. This procedure was repeated four times, circulating over the studies so that the model was trained and tested on the entire dataset. The mean score across the 4-fold tests were used as the final measure of performance. We scored the models by calculating the area under the receiver operating characteristic, (AUC-ROC) a summary metric of classification performance that take into account both sensitivity and specificity. Furthermore, AUC-ROC is not detrimentally affected by unbalanced data, that is the number of observations in each class. This was particularly important because each region varied in the ratio of studies that activated it to the studies that did not, and we wanted to ensure that our measure of performance was not driven by this variation.

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. For each cognitive concept, the odds-ratio was 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 computed a permutation test for each region by permuting 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-ratios for each cognitive concept, for each region individually. We then calculated p-values for the real log odds-ratios using this newly generated distribution and indicate which associations are significant at the p<0.001 threshold in Fig. 3.

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.

*Machine learning algorithms*. Scikit-learn (Pedregos et al., 2012) a python machine learning module, was used for all machine learning analyses in this study (PCA, k-means clustering, naive Bayes classification).

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**Figure Legends**

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) We functionally characterized each cluster by determining which cognitive functions best predicted their activation.

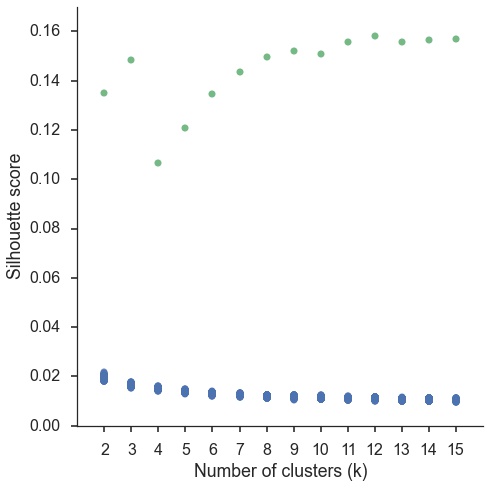
Figure 2. Co-activation-based k-means clustering of the medial frontal cortex at two levels of granularity. A) We identified three broad functional zones along a rostral-caudal axis. B) At a more fine-grained level, we identified nine sub-regions. SMA: supplementary motor area; SMAr: SMA rostral; SMAc: SMA caudal; pre-SMAc: caudal pre-SMA; pre-SMAr: rostral pre-SMA; dACC: dorsal anterior cingulate cortex; dACCc: dACC caudal; dACCr: dACC rostral; rACC: rostral anterior cingulate cortex; mPFC: medial prefrontal cortex; dmPFC: dorsal medial PFC; vmPFC: ventromedial PFC

Figure 3. Functional co-activation networks of medial frontal cortex zones (A) and sub-regions within each zone (B). We determined which voxels across the brain indicated a high probability that each parcel was active, controlling for other parcels in the same map. The three mFC zones showed distinct whole-brain co-activation patterns while sub-regions within each zone showed more fine-grained differences in co-activation. Images are presented using neurological conventions. Images were whole-brain corrected using false detection rate (FDR) at p <0.01. Co-activation pattern for each region is color coded in correspondence with Figure2.

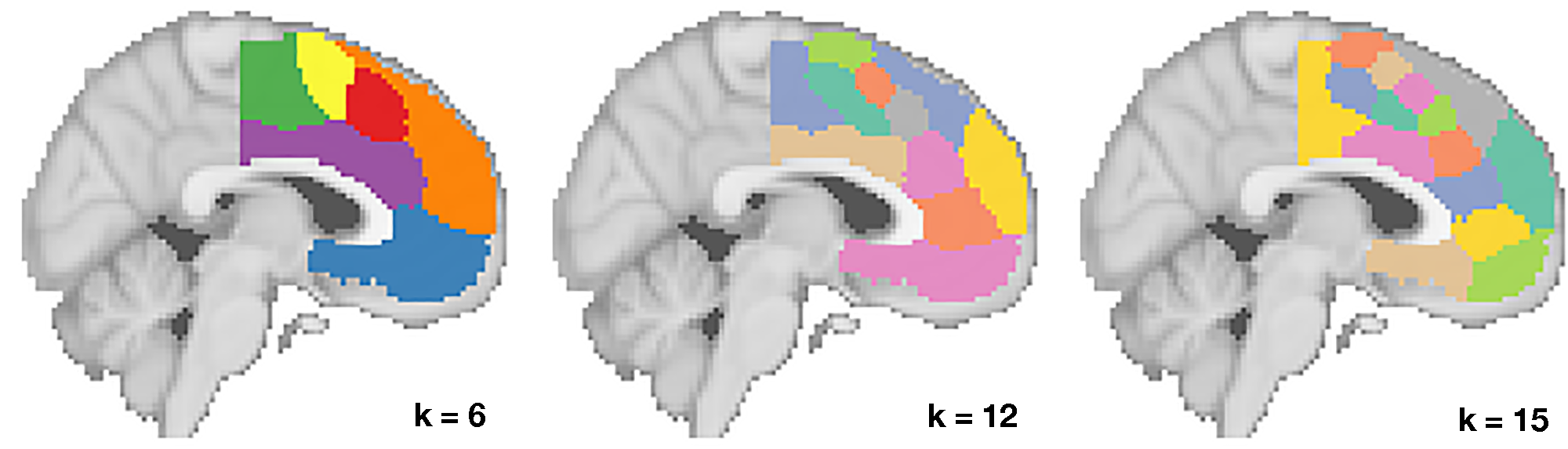
Figure 4. Functional specialization profile of each of the MFC clusters. Each cluster was individually profiled to determine which cognitive functions that best predicted its activation. Top) Each of the three functional zones we identified showed distinct functional profiles with broad shifts across cognitive domains Bottom three) Within each zone, each sub-region showed fine-grained shifts in functional specialization. Strength of association of each cognitive concept with each region is measured in log-odds ratio. We determined which cognitive concepts significantly predicted activation for each region using permutation testing. We indicate significant associations at the p<0.001 threshold with dots corresponding to each region next to each concept.

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

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 |