Functional specialization and complexity in medial frontal cortex

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 (Ball, Schreiber, Feige, Wagner, & Lücking, 1999; Kennerley & Sakai, 2004; Lee, Chang, & Roh, 1999; Leek & Johnston, 2009; Roland, Larsen, & Lassen, 1980), while nearby dorsal anterior cingulate cortex (ACC) has been implicated in various aspects of cognitive control, such as conflict (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Milham et al., 2001; Rushworth, Walton, & Kennerley, 2004) and error processing (Brown & Braver, 2005; C. S. Carter et al., 1998; Holroyd, Nieuwenhuis, & Yeung, 2004), and is thought to be important region for pain processing (Rolls et al., 2003; Treede, Kenshalo, Gracely, & Jones, 1999; 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, Luu, & Posner, 2000; K. A. Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Winecoff et al., 2013), autonomic function (Critchley et al., 2003), and valuation (Bartra, McGuire, & Kable, 2013; Hare, Camerer, & Rangel, 2009; Rogers et al., 2004). Furthermore, portions of mPFC have also been associated with a variety of stimulus-independent internally oriented processes, such as mentalizing (Baumgartner, Götte, Gügler, & Fehr, 2012; Denny, Kober, Wager, & Ochsner, 2012) and autobiographical memory (Spreng & Grady, 2010; Summerfield, Hassabis, & Maguire, 2009).

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. Bush et al., 2000; Shackman et al., 2011) or restrict themselves to a small region of interest (e.g. Palomero-Gallagher et al., 2015). 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 (Poldrack, 2006). This concern is particularly acute in the case of MFC regions pre-SMA and dACC, suggesting low selectivity to a

given domain (Nelson, Dosenbach, Cohen, Wheeler, Schlaggar, & Petersen, 2010a; Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011).

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 (Yarkoni et al., 2011). 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 (Robinson, Laird, Glahn, Lovallo, & Fox, 2010; Smith et al., 2009; Toro, Fox, & Paus, 2008), revealing three distinct zones along the rostro-caudal axis which further fractionated into nine sub-regions. We characterized the cognitive profiles of these clusters using multivariate classification analyses and found that the three functional zones accounted for a large portion of functional variation; however, we also found fine-grained variation in functional specialization between sub-regions within a functional zone. Collectively, our results reveal considerable diversity in the functional roles of discrete MFC subregions, provide insight into the spatial topography of MFC at several different scales, and suggest that previous studies may have overstated the case for the convergence of different processes in MFC.

Results

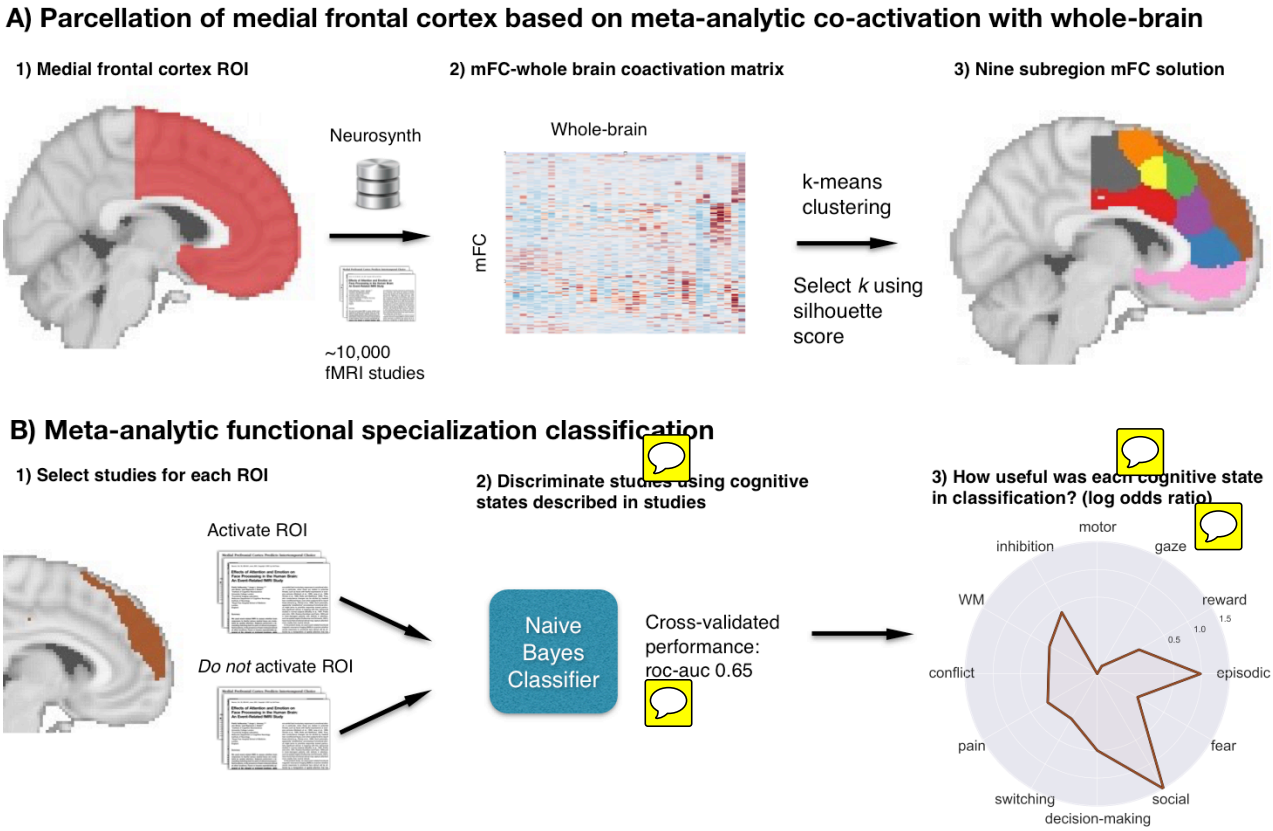


Figure 1. Methods overview. A) Co-activation with the rest of the brain for each voxel in medial frontal cortex ROI was calculated and used to create a distance matrix of MFC voxels; k-means clustering was applied to distance matrix resulting in spatially distinct clusters. B) We functionally characterized each cluster by determining which cognitive functions best differentiated studies that activated each cluster, from those that did not.

Functionally separable components of medial frontal cortex

Our first goal was to identify functionally dissociable spatial regions in the human medial frontal cortex (Figure 1A). Our MFC region of interest (ROI) spanned the entire medial surface of frontal cortex bilaterally, including the entirety of the supplementary motor area (SMA), pre-SMA, anterior cingulate cortex, medial prefrontal cortex, and medial aspects of the frontopolar and orbitofrontal cortex. We identified putatively separable divisions of medial frontal cortex on the basis of shared co-activation profiles with the rest of the brain (Toro et al., 2008; Smith et al., 2010; Chang et al, 2013). This approach exploits the likelihood of a voxel co-activating with another voxel across studies in the meta-analytic database, analogous to the functional coupling of individual voxels across time in resting state functional connectivity MRI (rs-fMRI) analyses. Because

structure-to-function mappings can be identified at multiple spatial scales, we iteratively extracted 2- through 15-cluster solutions. We asses the validity of these different solutions by calculating the silhouette score—a commonly use measure of inter-cluster coherence. Permutation analyses indicated that the null hypothesis of random clustering could be rejected for all solutions ($p < .001$), with silhouette scores reaching local maxima at 3 and 9 clusters; silhouette scores plateaued after 9 clusters, reaching an absolute maximum at 12 clusters (SI Figure 1). We focus here on the 3- and 9-cluster solutions, which provide insight into the functional topography of MFC at two different scales: broad functional zones and fine-grained regions. Figures for 6, 12, and 15 clusters are available in the supplemental material (SI Figure 2).

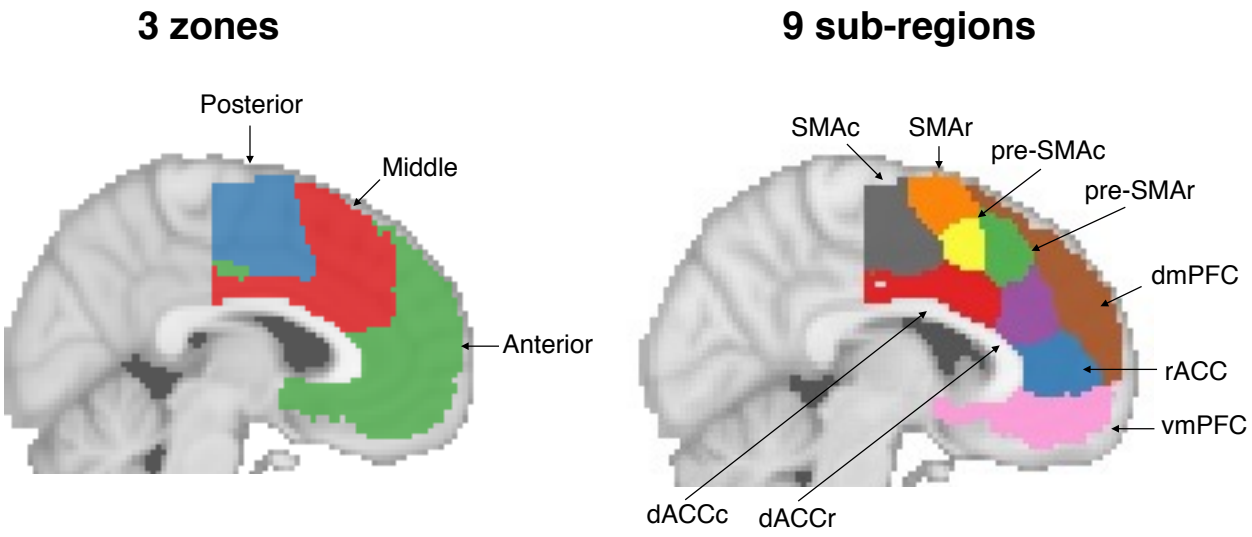


Figure 2. Co-activation-based k-means clustering of the medial frontal cortex at two levels of granularity. Voxels in the MFC were grouped together based on similarity of co-activation with all other voxels in the brain. A) At a coarse level, we identified three functional zones along a rostral-caudal axis. B) At a more fine-grained level, nine regions sub-regions were identified. 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

At the coarsest level, medial frontal cortex divided into three broad bilateral zones (Figure 2A). Although the k-means clustering algorithm imposed no spatial constrains, we observed an orderly parcellation of MFC into three distinctive zones along the rostral-caudal axis. We refer to these as the posterior, middle and anterior zones. The posterior zone encompassed regions that have been previous associated with sensorimotor function, such as the paracentral lobule, SMA, and dorsal posterior midcingulate cortex. The posterior and middle zones delineated from each other

around 6 mm rostral to the vertical commissure anterior (VCA) line, consistent with definitions of pre-SMA (Picard and Strick, 1996; Rizzolatti, Fadiga, Matelli, Bettinardi, Paulesu, Perani, & Fazio, 1996; Kim et al., 2011). The middle zone also included much of dorsal anterior cingulate (dACC) running along the corpus callosum (Vogt et al., 2005). The anterior zone encompassed a large portion of medial prefrontal cortex, including rostral and subgenual aspects of anterior cingulate cortex, and medial aspects of orbitofrontal cortex and the frontal pole.

The nine-cluster solution revealed additional fine-grained topographical organization, with each of the three major zone fractionating in an orderly way into 2-4 smaller regions (84% of all voxels within each major zone overlapped with its putative subregions) (Figure 2B). Lying roughly within the posterior zone, we found two clusters consistent with cytoarchitectonic-based rostral and caudal subdivisions of SMA (Vorobiev & Luppino, 1998; Luppino, 1993). Within the middle functional zone, we found four subregions: two lying dorsal of the cingulate sulcus, and two lying neatly in the anterior cingulate cortex proper. We refer to the two dorsal clusters pre-SMA, caudal and rostral, as they are positioned at least 6mm rostral of the VCA line, consistent with cytoarchitechtonic definitions of pre-SMA (Picard and Strick, 1996; Rizzolatti, Fadiga, Matelli, Bettinardi, Paulesu, Perani, & Fazio, 1996; Kim et al., 2011). The two dorsal clusters were consistent with prior cytoarchitechtonic evidence suggesting that dorsal ACC (also known as midcingulate cortex) fractionates into caudal and rostral subdivisions and does not extend dorsally past the paracingulate sulcus (Vogt et al., 2005). The anterior functional zone fractionated into clusters encompassing rostral anterior cingulate cluster (rACC), and dorsal and ventral subdivisions of mPFC. rACC delineated from vmPFC in a manner consistent with cytoarchtechtonic parcellations (Vogt et al., 2015), although at this level of resolution subgenual ACC did not form its own cluster and instead was grouped with medial orbitofrontal cortex into a ventral mPFC (vmPFC) cluster (but see 12-region solution: SI Figure 1). Finally, dorsal mPFC (dmPFC) 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 and 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.

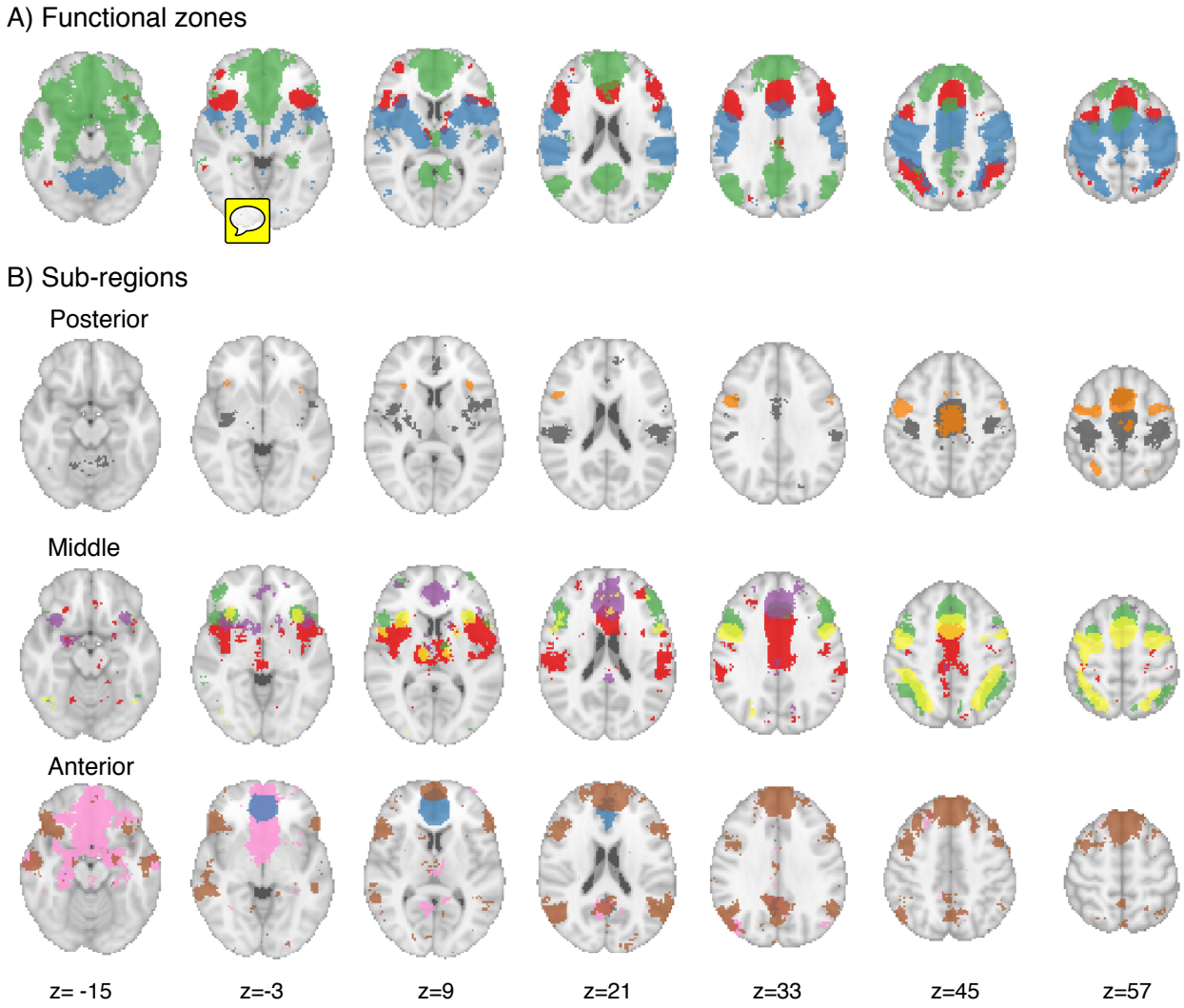


Figure 3. Functional co-activation networks of medial frontal cortex zones (A) and sub-regions within each zone (B). We determined which voxels across the brain indicated a high probability that each parcel was active, controlling for other parcels in the same map. The three mFC zones showed distinct 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 Figure 2.

First, we mapped the whole-brain co-activation patterns of the three functional zones, controlling for co-activation in other MFC zones, and identified distinct patterns for each (Figure 3; $p < 0.01$, FDR whole-brain corrected). The posterior zone (blue) showed robust bilateral co-activation with lateral motor regions, lateral parietal cortex, the anterior lobe of the cerebellum, the thalamus and putamen, consistent with an important role in motor function. The posterior zone also co-activated with posterior insula, an important region for sensorimotor, somatosensory and

pain processing (Chang et al., 2013). The co-activation pattern for the middle zone resembled an anterior-shifted version of the posterior zone's co-activation pattern, robustly co-activating with more anterior aspects of the thalamus, dorsolateral prefrontal cortex and anterior aspects of the insula—regions known to be important for high-level cognitive processes, including cognitive control (Banich, 2009; Carpenter, 2000; L. J. Chang, Yarkoni, Khaw, & Sanfey, 2013). Finally, the anterior functional zone showed a qualitatively different pattern of co-activation, suggesting this region is involved with a different class of cognitive processes as the former regions. The anterior zone primarily co-activated with regions in the default network hypothesized to support internal mentation, memory such as bilateral posterior cingulate cortex, precuneus, angular gyrus and the hippocampus (Andrews-Hanna, 2012). The anterior zone also showed robust co-activation with regions known to be important for affective processing, such as the amygdala and ventral striatum.

Next, we calculated the functional co-activation networks for each sub-region, controlling for co-activation patterns in the other sub-regions in its corresponding functional zone (Figure 3B). In the posterior zone, caudal SMA showed greater co-activation with lateral somatosensory cortices and posterior insula / operculum, suggesting rostral SMA may be more involved in processing sensory afferents involved in motor function. In contrast rostral SMA showed greater co-activation with posterior aspects of lateral prefrontal cortex, extending anteriorly into the inferior frontal junction (IFJ) as well as greater co-activation with anterior insula, regions associated with higher-level cognitive functions such as stimulus-response mapping (Brass, Ullsperger, Knoesche, Cramon, & Phillips, 2006) and goal-directed cognition (L. J. Chang et al., 2013; Nelson, Dosenbach, Cohen, Wheeler, Schlaggar, & Petersen, 2010b).

Within the middle zone, we found that all four sub-regions strongly co-activated with various aspects of the insula, consistent with previous studies suggesting the dorsal ACC and anterior insula are tightly coupled as part of the so-called "salience network" (Seeley et al., 2007) or "cingulo-opercular network" (Power & Petersen, 2013). However, caudal dACC more strongly co-activated with the operculum and posterior insula, regions implicated in painful experiences (Segerdahl, Mezue, Okell, Farrar, & Tracey, 2015); moreover caudal dACC also co-activated with SII and the brain stem, consistent with work highlighting the importance of this region--also known as the cingulate motor zone-- in precise movement (Paus, 2001; Picard & Strick, 1996) and work implicating dACC in pain processing (Vogt, 2005; Wager et al., 2013). In contrast, rostral dACC co-activated more strongly with ventro-anterior portions of the insula, which has been previously associated with the processing of chemosensory information such as gustation and olfaction

(Yaxley et al. 1990; Pritchard et la., 1999). Rostral dACC also showed co-activation with lateral posterior OFC (lpOFC)—a region known to be important for decision-making and reward-driven learning (Elliott, Dolan, & Frith, 2000; Schoenbaum & Roesch, 2005). In contrast, both pre-SMA clusters were strongly associated with dorso-anterior insula and regions in the frontoparietal control network, such dorsolateral prefrontal cortex (DLPFC) and the superior parietal cortex (SPC). However, rostral pre-SMA's co-activation extended further anterior into dorsolateral aspects of 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 (Badre & D'Esposito, 2009).

Within the anterior functional zone, we found that rACC did not show many significant differences in co-activation from its neighboring regions, suggesting rACC may be primarily involved with local processing within the anterior functional zone. In fact, both dmPFC and vmPFC showed greater co-activation with PCC, another key area in the default network. dmPFC showed strong co-activation with regions in the so called 'mentalizing' network known to be important for social processing , such as the tempo-parietal junction (TPJ) (R. M. Carter & Huettel, 2013), superior temporal sulcus (STS) (Zilbovicius et al., 2006). dmPFC also showed robust co-activation with bilateral inferior frontal gyrus (IFG), a region important for language processing and inhibition as well as posterior middle frontal gyrus. Finally, vmPFC showed strong co-activation with regions in the mesolimbic dopamine system, such as ventral striatum, as well as subcortical regions important for affective processing such as the amygdala, extending into the hippocampus. As a whole, these functional co-activation patterns suggest the three broad functional zones in MFC are likely to exhibit substantial functional differences whereas sub-regions within each zone are likely to show more fine-grained differences in functional specialization.

Meta-analytic functional specialization

Next, we sought to determine if the putatively functionally separable MFC regions we identified using co-activation data exhibited differences across the wide-variety of cognitive states represented in the Neurosynth database. In contrast to traditional meta-analyses that investigate the whole-brain neural correlates of theoretically motivated cognitive functions selected *a priori* (e.g. pain and cognitive control in dorsal ACC), we used a data-driven approach that surveyed a broad range of cognitive states and identified those most strongly predictive of MFC cluster activity. To characterize the functional specialization of different MFC clusters, we used a machine learning classifier to identify the cognitive states that best predicted the activation of each individual cluster.

We used a set of 34 cognitive concepts derived by applying a standard topic modeling approach to the text of articles in the database (Poldrack et al., 2012), allowing us to also sidestep the difficult problem of manually defining a cognitive ontology and ensuring our analysis was as data-driven as possible (See Supplemental Table 1 for full list of derived topics). For each cluster individually, we divided the Neurosynth database into two non-overlapping sets of studies: those that reported activation within the cluster and those that did not (Figure 1B). We then trained a naïve Bayes classifier to differentiate the two sets of studies on the basis of the cognitive concepts discussed within each study. From the resulting fitted models, we extracted the log-odds ratio of each cognitive concept given activation of that cluster, revealing the cognitive concepts that best predicted activity for each individual MFC region.

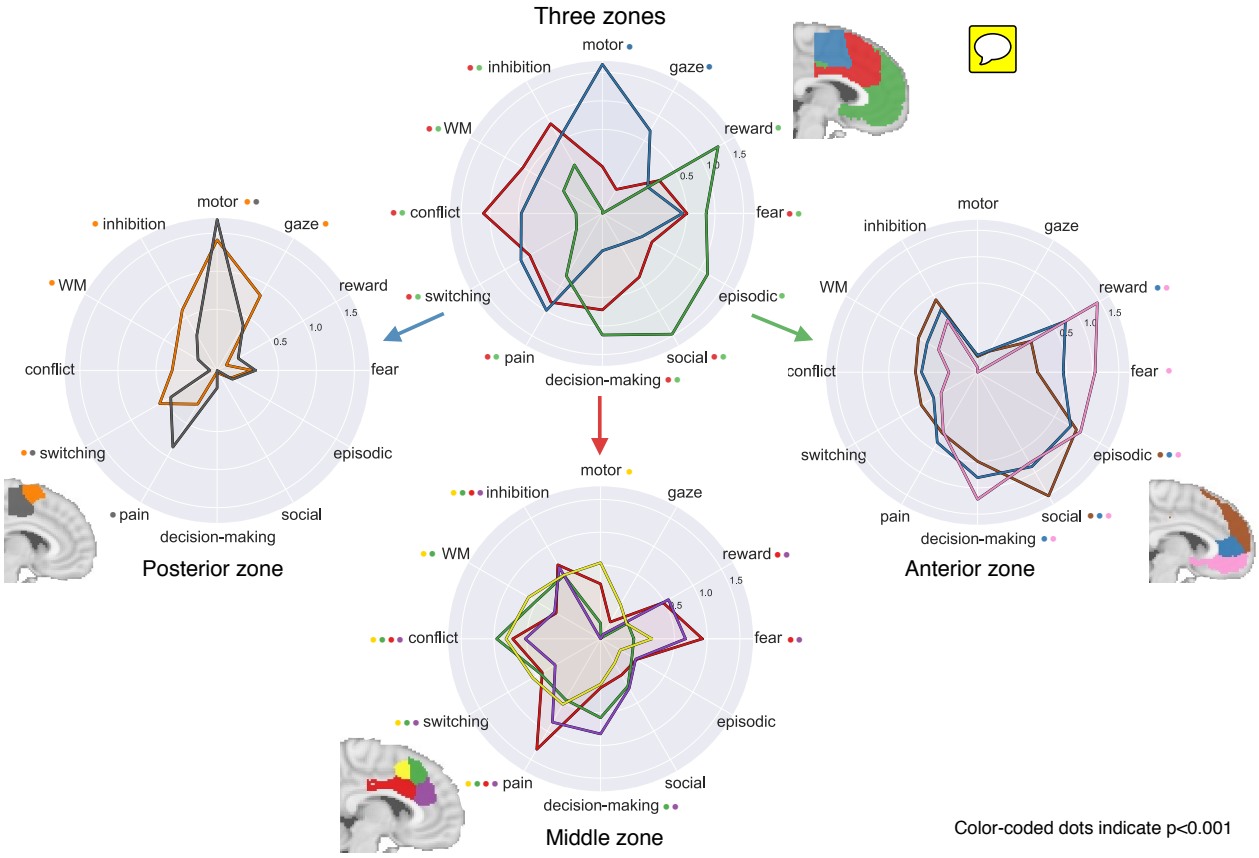


Figure 4. Functional specialization profile of each of the MFC clusters. Each cluster was individually profiled to determine which cognitive functions that best predicted its activation. Top) Each of the three functional zones we identified showed distinct functional profiles with broad shifts across 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.

Across the three coarse functional zones we identified in MFC, we observed distinct patterns of functional specialization, consistent with their divergent patterns of functional co-activation (Figure 4). The posterior zone was strongly and primarily involved with motor function, including gaze and eye movements, consistent with its robust co-activation with primary motor cortex. The middle zone showed a distinct shift away from motor function. This zone was primarily associated with various facets of cognitive control (e.g. conflict, working memory, inhibition, switching), but was also predicted by affective processes such as pain, reward, decision-making. The anterior functional zone showed a distinct shift away from externally oriented processes such as motor function and cognitive control and was strongly associated with affective processes, such as reward, fear and decision-making, as well as social processing. This qualitative difference in functional specialization is consistent with the distinct pattern of functional co-activation we observed for the anterior zone in our previous analysis.

Next, we investigated the functional specialization of within each of these functional zones at a more fine-grained level of analysis by profiling the functional specialization of each of nine subregions we identified and comparing the functional specialization of sub-regions within a functional zone. Overall, subregions within each cluster showed similar profiles to each other, with subtle yet important distinctions in their functional specialization. In the posterior functional zone, both were similarly involved in motor function as well as switching; however, only caudal SMA was associated with pain processing, whereas rostral SMA showed significant associations with working memory (WM), inhibition and gaze function.

All four subregions of middle functional zone we identified were involved with cognitive control to varying extents, although on average, pre-SMA was more strongly associated with cognitive control. Working memory in particular was strongly associated with pre-SMA--peaking in caudal pre-SMA-- while switching and conflict were more evenly associated with all four subregions in this zone. The sole exception was inhibition, which was more strongly associated with dACC than pre-SMA. Both dACC clusters were further characterized by a strong association with affect, including pain, fear and reward. Of these three, pain significantly predicted activity in all four subregions, although pain was more strongly associated with dACC than pre-SMA. Our analysis also revealed differences between the rostral and caudal sub-regions in the middle zone. Only caudal pre-SMA and dACC showed associations with motor function (only significant at $p<0.001$ in pre-SMA), while the two rostral clusters showed virtually no association. In contrast, only rostral pre-SMA and dACC were significantly associated with decision-making.

Regions within the anterior functional zone showed a distinct shift away from externally oriented processes, such as cognitive control, motor function and pain, and towards internal, self-oriented processes, such as decision-making, social processing, and episodic memory, and emotion. Again, the three subregions of this zone showed rather similar functional specialization patterns; in particular all three regions were similarly involved in emotion and episodic-memory. However, although all three sub-regions were significantly associated with social processing, this association peaked in dmPFC, consistent with previous meta-analysis (Denny et al., 2012). We observed a reverse pattern for reward and decision-making, as these processes were significantly associated with vmPFC and rACC. Finally, vmPFC was also associated with fear, consistent with its strong co-activation with the amygdala. However, this region was not activated for negative affect in a general was, as pain did not significantly predict vmPFC activity.

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) (Figure 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.

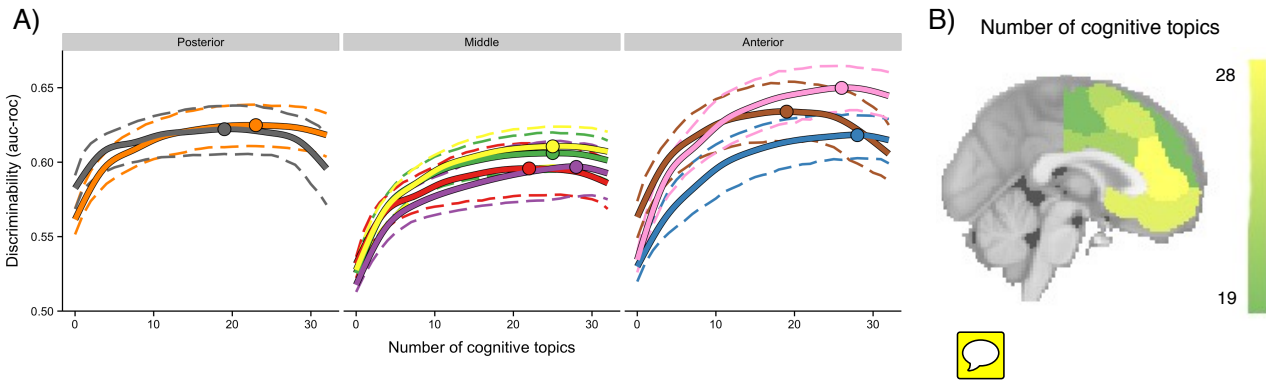


Figure 5. Functional complexity of MFC. (A) As the number of cognitive functions in the classifier increased (x-axis) discriminability of activity (y-axis) increased for all regions. However, regions varied in the number of topics required to reach maximum discriminability (noted by a circle). Bootstrapped 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.

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' (Figure 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 (Wager et al., 2013). 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 (Corbetta, Akbudak, Conturo, & Snyder, 1998; Everling & Munoz, 2000). 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)(C. S. Carter et al., 1998). 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 (Elliott et al., 2000; Schoenbaum & Roesch, 2005). 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' (Andrews-Hanna, 2012) 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 (Iacoboni et al., 2004; Mitchell, Banaji, & Macrae, 2006). Moreover, dmPFC showed strong co-activation with TPJ, a region thought to also be important for mentalizing (Baumgartner et al., 2012; Denny et al., 2012). 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 (Andrews Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; van den Heuvel & Sporns, 2013). 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 (Knutson, Adams, Fong, & Hommer, 2001) and amygdala (Fanselow & Galse 2003; R. G. Phillips & LeDoux, 1992) , respectively. However, vmPFC was also associated with higher-level cognitive processes that are known to depend on these affective signals, such as decision-making (Matthews, Simmons, Lane, & Paulus, 2004; Salamone, Correa, Mingote, Weber, & Farrar, 2006) and memory (Agren, Engman, Frick, Björkstrand, & Larsson, 2012; Hamann, Ely, Grafton, & Kilts, 1999). Importantly, although some have characterized vmPFC as being a 'valuation' system (Lebreton, Jorge, Michel, Thirion, & Pessiglione, 2009), 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 (Roy, Shohamy, & Wager, 2012).

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 (Poldrack et al., 2012), 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 (Cole, Yeung, Freiwald, & Botvinick, 2009; Paus, 2001). 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.

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 (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008) 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 (Figure 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.

Predictive modeling of activity using cognitive functions. 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 (Androutsopoulos, Koutsias, Chandrinos, Paliouras, & Spyropoulos, 2000). 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

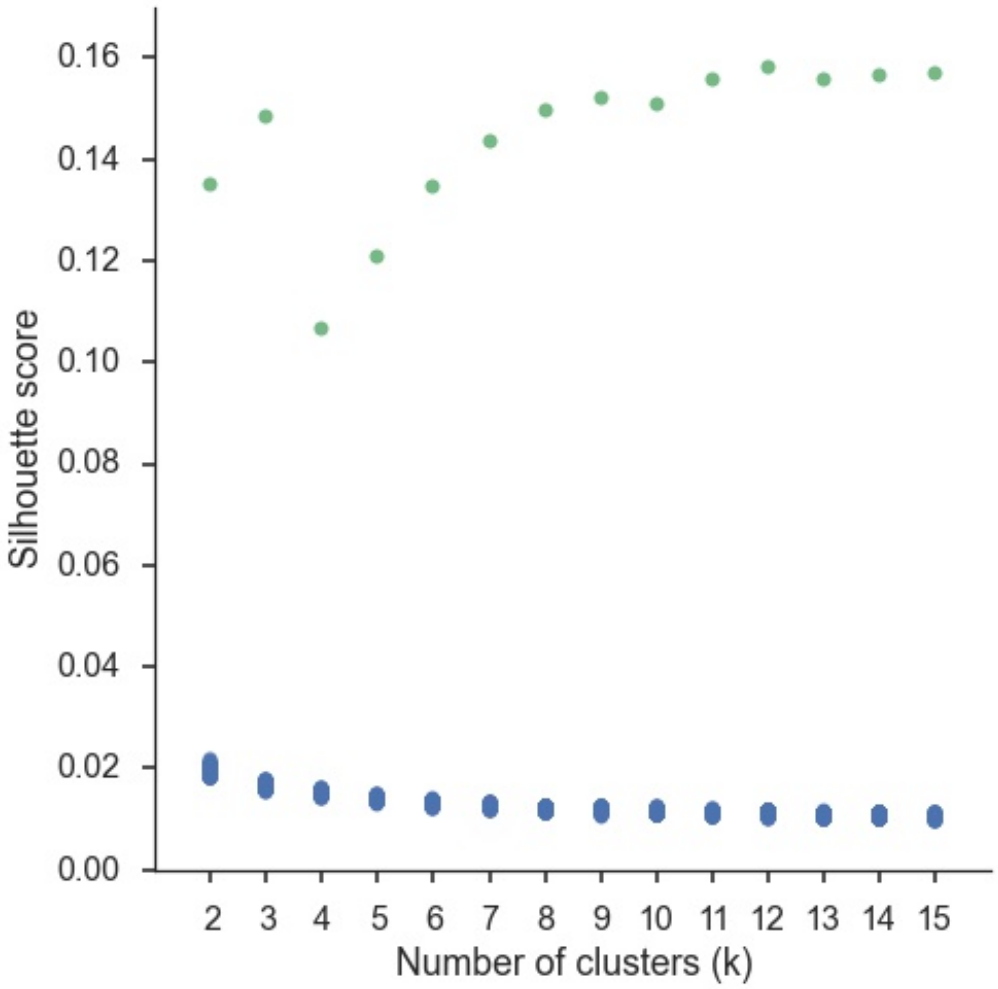
unbalanced data, that is the number of observations in each class. This was particularly important because each region varied in the ratio of studies that activated it to the studies that did not, and we wanted to ensure that our measure of performance was not driven by this variation.

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 Figure 3.

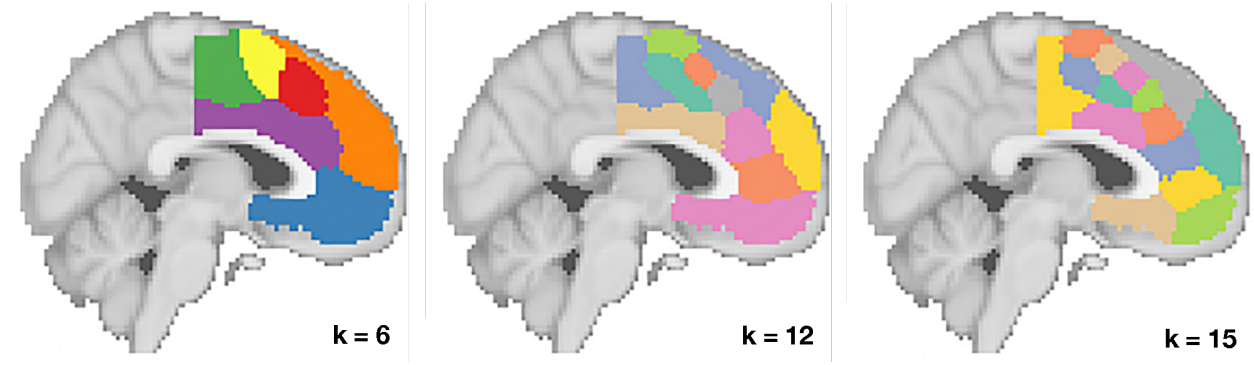
Functional complexity. We quantified the complexity of function in order to determine if MFC regions are involved in a diverse range of cognitive functions. We operationalized regions with heterogenous function as those that required a larger number of topics to accurately predict their activity, while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

Supplemental 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	sentences	comprehensi	sentence	language	syntactic

comprehension on					
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-Cognit*ive 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

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