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Journal Club

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Identifying Functional Subdivisions in the Medial Frontal Cortex

Pedro Silva Moreira, Paulo Marques, and Ricardo Magalhães

Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, 4710-057 Braga, Portugal, and Life and Health Sciences Research Institute/3B's, PT Government Associate Laboratory, 4710-057 Braga/Guimarães, Portugal

Review of de la Vega et al.

The medial frontal cortex (MFC) is thought to be involved in numerous sensorimotor, cognitive, and affective processes. This region is commonly divided into separate subregions, including the anterior cingulate cortex, supplementary motor area (SMA), and the pre-SMA, orbitofrontal cortex, and anterior frontal poles (Amodio and Frith, 2006). The activity of the MFC is highly heterogeneous. Activation of the MFC is reported in many fMRI studies, and it is associated with a variety of processes, including action monitoring (Bonini et al., 2014), response conflict (Gehring and Fencsik, 2001), reward (Taylor et al., 2006), and decision-making (Kahnt et al., 2011). This creates uncertainty in the identification of specific psychological states associated with patterns of activity in the MFC, referred as the reverse inference problem. This long-standing inferential problem arises because most neuroimaging studies aim to identify neural characteristics of specific manipulations, rather than determining which psychological states a given pattern of activity implies (Poldrack, 2006). The ability to perform reverse inferences is of upmost relevance for the fMRI research to establish a diagnostic of a particular state (i.e., to provide significantly greater specificity to neuroimaging findings), which is crucial for advancing our understanding of the mind and brain (Poldrack, 2006).

In a recent publication in *The Journal of Neuroscience*, de la Vega et al. (2016) sought to extend knowledge of the functional architecture of the MFC by performing a meta-analysis of ~10,000 studies from the Neurosynth platform, a large-scale database with automated synthesis of neuroimaging data (Yarkoni et al., 2011). Based on patterns of coactivation, the authors found that aggregating MFC voxels into three or nine divisions yielded the best clustering solutions. The tripartite organization divided the MFC in posterior, middle, and anterior zones. The 9-cluster solution further divided these zones into dissociable subregions: the posterior zone was divided into the supplemental motor area (SMA) and the pre-SMA; the middle zone, or midcingulate cortex, was divided into dorsal/ventral and anterior/posterior subregions; and the anterior zone was separated into dorsomedial prefrontal cortex, ventromedial prefrontal cortex (vmPFC), and pregenual anterior cingulate cortex. These zones presented distinct coactivation patterns with the remaining brain structures: the posterior zone was mainly associated with motor-related regions; the middle zone with the anterior thalamus and clusters from the frontoparietal control network; and the anterior zone with clusters from the Default-Mode Network. Finally, the authors modeled the topics of each study in the Neurosynth database and generated functional preference profiles by testing which topics from the semantic context of each study best predicted the activation of a given region, using a Bayesian classification approach. The activation of the posterior zone was associated with motor functioning; the middle zone with cognitive control, pain, and affect; and the anterior zone with reward, social processing, and episodic memory.

These results are complemented by the parcellation of the human cerebral cortex recently proposed by Glasser et al. (2016). One of the most prominent differences concerns the anterior part of the MFC, particularly the vmPFC, which was divided into more subregions in the Glasser et al. (2016) study (mainly associated with Default-Mode Network clusters). These differences might arise from methodological considerations pertaining to the strategy of parcellating the MFC. In the study from de la Vega et al. (2016), the 9-cluster

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Correspondence should be addressed to Pedro Silva Moreira, Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, 4710-057 Braga, Portugal. E-mail: pedromoreira@ecsaude.uminho.pt.

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solution was selected due to the stabilization of the silhouette coefficient (the minimum average distance between cluster members). However, no point of inflection was observed, opening the possibility that the maximum number of clusters considered (15) might not be enough to reveal more refined subdivisions of the MFC. It can be hypothesized that the vmPFC is composed of subregions that have distinct roles at rest, but function in coordination during affective processes, such as reward or fear. Indeed, when analyzing the results from de la Vega et al. (2016, their Fig. 4), it is evident that, although distinct subdivisions of the anterior MFC are indissociably linked to episodic memory, they are differently associated with reward. Therefore, it is reasonable to assume that these subdivisions may work either together or separately, depending on the functional context. Furthermore, it is also likely that regions with different properties, such as the ones explored by Glasser et al. (2016), coexist across psychological states by making part of the same circuit. Of note, none of the studies integrated structural connectivity for the parcellation of the MFC, which is thought to influence brain functional patterns (Park and Friston, 2013). Together, this suggests that the cortical organization of the MFC is still an open question and further developments can be expected in the near future.

de la Vega et al. (2016) suggest that the association of SMA with pain processing and motor function could reflect the importance of this region for initiating movement in response to pain. This is in accordance with previous reports of associations between activation in the SMA, motor control, and painful stimuli (Misra and Coombes, 2015). Despite falling within the same cluster for the tripartite solution, posterior subdivisions have dissociable structural links: whereas the SMA projects directly to motor areas, the pre-SMA projects to the dorsolateral prefrontal cortex (Wang et al., 2005). However, there seems to be no clear functional dichotomy or clear structural boundary between the SMA and pre-SMA subdivisions, but rather a continuum that does not favor a modular organization (Nachev et al., 2008).

de la Vega et al. (2016) also suggested that the dorsal clusters from the middle zone were more associated with cognitive motor control that requires working memory, whereas the ventral clusters' function would be to incorporate low-level affective signals into cognitive control. Despite agreeing with previous findings reporting an involvement of the mid-cingulate cortex in pain processing (Vogt, 2016), these results seem to suggest that dorsal clusters share functional commonalities with the posterior MFC, whereas anterior subdivisions are more related with the anterior MFC. Again, this raises the question of the extent to which the MFC should be considered as an agglomerate of functionally distinct subparts and whether the functional division depends on the functional context. Critically, de la Vega et al. (2016) suggest that the anterior zones of the MFC (particularly the pregenual anterior cingulate cortex and the vmPFC), in comparison with other MFC subdivisions, are more associated with affective processes and decision-making. This supports the view of Euston et al. (2012) that the role of the anterior MFC is to produce adaptive emotional responses based on inputs from emotion-related structures and storing the appropriate actions.

Some methodological points should be considered. The authors used generative topic modeling to define a set of topics based on the co-occurrence of key words across the abstracts of fMRI studies. de la Vega et al. (2016, their Table 1) demonstrated some words loaded on multiple topics (e.g., "cognitive" loaded on three topics: conflict, inhibition, and working memory), which may explain why all the subregions of the middle portion of the MFC were similarly predicted by inhibition and response conflict (de la Vega et al., 2016, their Fig. 4). As recognized by the authors, the use of standardized ontologies (e.g., Poldrack et al., 2011) might constitute an improvement on the reliability of psychological concepts. Ultimately, this may help to further clarify the link between individual subregions of the MFC and their functional correlates.

Despite the valuable efforts of the study by de la Vega et al. (2016) to address the reverse inference problem associated with the MFC, it is important to be aware that their conclusions were based on forward inferences. Thus, future studies should focus on predictive models in which psychological states are classified based on the pattern of activation of individual MFC subdivisions, rather than using the psychological states to predict patterns of MFC activity. This would allow researchers to properly tackle reverse inferences (i.e., to infer that the pattern of MFC activation affects a specific function).

Recent debates in fMRI research have focused on the huge rate of false positive findings (Eklund et al., 2016) and the reduced chance of results' reproducibility (i.e., statistical power) (Button et al., 2013). Although scarcely used in fMRI research, the use of planned power analysis may improve the level of evidence in this type of study (Mumford, 2012). Notwithstanding, as de la Vega et al. (2016) highlight, the meta-analytic approach implemented in their study was exclusively based on the aggregation of results reported as significant across studies. This is because the results of most neuroimaging publications are presented as tables with the coordinates of significant findings, which can be particularly problematic because it is likely that subthreshold, but consistent, effects across studies will not be captured when aggregating results (Gorgolewski et al., 2015). Thus, this work highlights the importance of sharing full statistical maps in individual neuroimaging studies to allow more refined estimation, through the use of image-based meta-analysis.

In conclusion, the study by de la Vega et al. (2016) is an important advancement in our understanding of the functional architecture of the MFC. Furthermore, it provides a great incentive for the development of strategies to solve a common concern in fMRI studies: the reverse inference problem. From a general perspective, the use of similar approaches may promote a more comprehensive understanding of the link between brain structures and their functional role, which is of upmost relevance to illuminate potential therapeutic targets in clinical populations.

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