Literature Review Paper Proposal Draft

**Abstract**

The medial prefrontal cortex (mPFC) has been associated with a variety of seemingly disparate functions. At the same time, certain functions ascribed to mPFC have been reported in spatially distal parts of this region. Accounts of mPFC function have been hampered by the lack of consensus on its functional spatial organization. A coherent fine-grained topographical map of mPFC would provide a foundation for future accounts of its function. Presently, I propose applying clustering algorithms on meta-analytic data from the BrainMap project. Unlike existing topographical maps, the present map will be clustered based on task-related data, rather than connectivity. Presumably, the organization revealed will be more sensitive to differences in function. I will critically compare the resulting map with various proposed organizational schemes in the literature. Then, to further probe mPFC’s function, I will use classification algorithms to determine which sub-regions differentiate classes of tasks. This analysis will focus on the differences between mental processes, rather than the overlap between them. Finally, I will critically compare these results to differential predictions made by existing accounts in the literature. This endeavor will help base future accounts of mPFC function on a data-driven organizational scheme based on actual task-related function.

**Introduction**

Unlike some regions of the brain, such as visual areas, there is a lack of consensus on the function of the medial prefrontal cortex (mPFC). This is partly due to the wide-range of functions that have been associated with it in fMRI studies. For example: action valuation, conflict monitoring, self-reflection, mentalizing, social processing, emotion regulation, and memory are all thought to involve mPFC. Two ways of accounting for this diversity of function is that mPFC is either a heterogenous region or that it subserves a more general function that encompasses all of the above functions. Researchers have tried to accomplish the latter by giving mPFC function broad labels to such as “valuation” or “affect”. However, the mPFC is quite a large regions and these underspecified hypotheses do not accurately account for the broad range of functions that mPFC encompasses.

More recently research has proposed that mPFC serves as a “hub” which connects various subservant regions and integrates information across them. This is supported by graph-analytic analyses of resting state functional connectivity MRI data, in which anterior mPFC is shown to have a higher level of “betweenness centrality” (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). In addition, a recent review proposed that ventromedial PFCserves as a hub that represents the “meaning” of complex situations, evaluates them with regards to prior experience and translates them into appropriate physiological and affective responses. In particular, using meta-analytic data from NeuroSynth, the authors conclude that a more dorsal region of vmPFC, the “simulation” system, processes the contextual meaning of the situation while a more ventral region, the “affect generation” system projects to subcortical regions which enact the affective response (Roy, Shohamy, & Wager, 2012).

While these recent proposals have helped us understand how mPFC is involved in such a large range of processes, a more fine-grained understanding is still needed. In particular, there are two outstanding problems. First, there is large variability reported in the location of activation for particular processes, such as “valuation”. Existing accounts of mPFC function make coarse predictions regarding the function spatial organization of mPFC. However, there is not a comprehensive fine-grained account that explains the spatial variability observed in the literature. Second, while “hub” accounts ascribe the variety of mPFC dependent processes on a common function, it is not known if these different processes can be differentiated on the basis of mPFC activity. This question is especially pertinent because the divisions of mPFC that have proposed (as in Roy et al.) occupy large portions of cortex. It stands to reason that within the proposed hubs there is a finer-grained spatial organization, which may discriminate the type of process that is occurring. Thus, while at a large-scale mPFC’s spatial organization may be explained on the basis of the commonalities between a large range of processes, it is likely there is a finer organization. Understanding this detailed spatial organization may help explain the observed spatial variability in activation.

A candidate class of methods to elucidate mPFC’s topographical organization is data-driven clustering techniques. These methods typically take a profile of connectivity between seeds in the region of interest and the rest of the brain. Based on this information, the various seeds are divided into clusters using a variety of algorithms. While these techniques have been fruitful in generating unbiased data-driven topographical maps of the brain there are two major limitations with regards to mPFC. First, while regions of mPFC have been parcellated, it has been typically as part of broader analyses that focused on other regions (e.g., parcellation of the cingulate, orbitofrontal cortex, or the whole brain). Thus, the mPFC as a whole has been not been focused on as a target of clustering analyses and certain boundaries between potential sub regions have not been directly tested. Second, most of these analyses use connectivity data from either resting-state functional MRI or DTI. This data can be helpful in dividing regions of cortex. However, these methods are blind to the actual function of these areas. It is plausible that certain adjacent areas differ in function but have very similar profiles of connectivity and such methods would fail to characterize interesting differences between them. This is a problem in particular with the mPFC because most of its connections are intrinsic or to nearby PFC regions.

A solution to these limitations is to cluster mPFC on the basis of its observed activation with respect to task type. Thus, the clustering that is obtained is not on the basis of connectivity, which may or may not be directly linked to function, but the region’s profile of task-related activation instead. This approach can elucidate differences with respect to behaviors that we think are theoretically interesting and may not be revealed by connectivity profiles. A way to implement this approach is toapply clustering methods on large-scale metaanalytic databases. A strong candidate is the BrainMap database, a collection of over 2000 papers and 84,000 activations. As the first step of this project, I plan to do so and critically assess the results with respect to existing clustering analyses of mPFC. It will be of interest to note the extent to which these approaches differ and if the activation-based clustering reveals a more fine-grained topography for mPFC. In addition, given that the source data encodes the type of paradigm that elicited the observed activity, it will be possible to use this meta-data to characterize the function of the resulting clusters.

While this analysis will provide a foundation for understanding mPFC’s functional organization, there are some overarching limitations to clustering analyses. In particular, it is not clear that clustering is even an appropriate way to characterize the function of the human brain. While there are some clear functional divisions in cortex, such as the motor strip versus the somatosensory strip, at a finer grain there may not be clear borders between functionally distinct regions, especially in pre-frontal regions. In addition, it is difficult to determine the correct number of clusters. Clusters are only valuable insofar as they help our understanding of the brain, but they are not likely to be respected by nature. In addition, mPFC, given its great amount of intrinsic connectivity and aforementioned variability in spatial activation, may be particularly problematic to parcellate into distinct clusters. Thus, in order to further probe the organization of mPFC without assuming distinct spatial divisions, a different approach must be taken.

The last part of this project will attempt to determine, which regions of mPFC *distinguish* different classes of tasks. This differs from many current methods that normally try to determine common areas of activations between similar tasks. It is possible to visually determine how different types of tasks differ. However, it is much more informative and analytically rigorous to test specifically which regions of mPFC are most predictive of different classes of mental processes. This can be tested using classification techniques, which determine if activation in a given sub-region is predictive of one process versus another. This analysis will allow us to distinguish different mental processes despite their overall commonalities in the mPFC. In order to make this approach fruitful, it will be important to select theoretically interesting comparisons to make. Part of this project will be to select these comparisons on the basis of a thorough reading of the literature. I plan to formulate these comparisons throughout the previous steps.

**Plan Summary**

In sum, this project aims to further characterize the functional spatial topography of the medial prefrontal cortex on the basis of task related activation. This will be done by generating a data-driven topographic map of mPFC using clustering algorithms based on the BrainMap database. I will then compare the results of this analysis with existing connectivity based parcellation schemes. In order to inform this critical analysis, I will perform a literature search on existing accounts of mPFC functional topography. This literature will help inform key theoretical comparisons of different classes of mental processes that both rely on mPFC but may be differentiated on the basis of their pattern of activation. I will then test these comparisons using classification algorithms on the NeuroMap database. In the end, I will base the framing of the final literature review given the outstanding questions that I found in the literature and was able to answer. Undoubtedly, the methods presently employed will only be able to answer a subset of the outstanding questions and I will narrow my literature review to focus on those aspects.