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# Co-activation based parcellation of the human frontal pole

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ABSTRACT

Historically, the human frontal pole (FP) has been considered as a single architectonic area. Brodmann's area 10, in the frontal lobe with known contributions in the execution of various higher order cognitive processes. However, recent cytoarchitectural studies of the FP in humans have shown that this portion of cortex contains two distinct cytoarchitectonic regions. Since architectonic differences are accompanied by differential connectivity and functions, the frontal pole qualifies as a candidate region for exploratory parcellation into functionally discrete sub-regions. We investigated whether this functional heterogeneity is reflected in distinct segregations within cytoarchitectonically defined FP-areas using meta-analytic co-activation based parcellation (CBP). The CBP method examined the co-activation patterns of all voxels within the FP as reported in functional neuroimaging studies archived in the BrainMap database. Voxels within the FP were subsequently clustered into subregions based on the similarity of their respective meta-analytically derived co-activation maps. Performing this CBP analysis on the FP via k-means clustering produced a distinct 3-cluster parcellation for each hemisphere corresponding to previously identified cytoarchitectural differences. Post-hoc functional characterization of clusters via BrainMap metadata revealed that lateral regions of the FP mapped to memory and emotion domains, while the dorso- and ventromedial clusters were associated broadly with emotion and social cognition processes. Furthermore, the dorsomedial regions contain an emphasis on theory of mind and affective related paradigms whereas ventromedial regions couple with reward tasks. Results from this study support previous segregations of the FP and provide meta-analytic contributions to the ongoing discussion of elucidating functional architecture within human FP.



## Introduction

The frontal pole (FP) of the human brain, often referred to as BA 10, is situated in the most rostral curvature of the cerebral cortex. During hominid evolution, this region experienced a differential reorganization in apes and humans, and subsequently encompasses a significantly larger proportion of the cortex in humans than in other species (Öngür et al., 2003; Semendeferi et al., 2001, 2011). This region continues to develop deep into adolescence in humans and has been shown to play a crucial role in a diverse range of higher order cognitive functions, including many adapted behaviors claimed to be "human-specific" (Duncan, 2010; Kovach et al., 2012; Ramnani and Owen, 2004; Waskom et al., 2014).

Anatomical definition of the FP was guided by a combination of post-mortem human and nonhuman primate histology and cytoarchitectural studies. Brodmann's (1909) classic cytoarchitectural definition of BA 10 encompassed a wide area of 6-layer granular isocortex located on the rostral surface of the frontal lobe as well as the contiguous region along the medial wall of the hemisphere. Brodmann's definition (as adopted by Talairach and Tournoux, 1988) has been widely employed in neuroimaging and neuropsychological research. However, treatment of the anatomically defined FP as a single homogenous area, without respect to its' functional properties, likely masks a more detailed regional

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specificity within the rostral frontal cortex. Furthermore, functional boundaries of this region have been highly variable across studies, leading to inconsistencies in their resultant functional properties. Indeed, a recent cytoarchitectural study of the FP in humans (Bludau et al., 2014) showed that the frontopolar cortex contains two distinct cytoarchitectonic regions. This mapping study distinguished between a region on the rostral surface of the frontal lobe that they labeled area Fp1, and an area located along the mesial surface of the superior frontal gyrus that they labeled Fp2. Cytoarchitecturally, Fp1 shows higher cell density in layer II and in lower parts of layer III, and a broader layer IV than area Fp2. Thus, in a region that was once thought to be cytoarchitecturally homogeneous (Dumontheil et al., 2008), we now have evidence to the contrary, which suggests that there may be functionally discrete sub-regions of the FP.

In addition to using cytoarchitectural differences to subdivide a region, it is also possible to distinguish cortical areas based on their patterns of connectivity. For example, fiber tracing studies in the marmoset and the macaque monkey have indicated that areas within the FP possess different anatomical connection patterns (Burman et al., 2011; Petrides and Pandya, 2007). These connectional differences are further supported by diffusion tensor imaging (DTI) findings in humans that indicate that the FP can be divided into sub-regions based on connection patterns (Liu et al., 2013). Using a clustering procedure, Liu performed a connectivity-based parcellation and defined three subregions of the frontopolar cortex and neighboring transitional area of the extreme rostral orbitofrontal cortex.

It is also possible to parcellate regions based on differences in functional connectivity patterns. Connectivity-based parcellation techniques can be applied to resting-state fMRI data to identify subregions within an ROI based on differences in voxel-wise time-series correlations between the seed and the whole-brain. Most previous efforts to identify functional distinctions within sub-regions of the FP were carried out, however, before quantitative coordinate-based meta-analytic methods were made available (Christoff and Gabrieli, 2000; Gilbert et al., 2006, 2010). More recently, a robust and task-dependent approach for investigating connectivity between brain regions has emerged with the advent of meta-analytic connectivity modeling (MACM) (Eickhoff et al., 2010; Laird et al., 2009b; Robinson et al., 2010). This technique mines the co-activation patterns reported across hundreds of published neuroimaging studies archived in the BrainMap database (http://brainmap.org) in order to determine the task-based functional connectivity of brain regions. This data-driven parcellation technique provides a complementary approach toward the delineation of cortical modules (Muhle-Karbe et al., 2014). The methodology is motivated by the notion that the function of a brain region is ultimately constrained by its connections with other areas (Passingham et al., 2002) known from monkey and cat axonal tracing, which implies that functional units should be distinguishable based on the dissimilarity of their connections. Bludau et al. provided a preliminary MACM in which they tested whether FP areas defined by probabilistic locations of FP1 and FP2 showed different patterns of co-activation. Their results showed definite regional differences, however they did not test whether a parcellation based on task-based functional connectivity follows similar contours as their cytoarchitecturally defined areas.

Although structure and function are closely related in brain architecture, there is not necessarily a one-to-one relationship between them. Instead, it is possible for differential functional zones to exist even within an area that shares gross similarities in cytoarchitecture. This occurrence has been noted in previous studies examining the prefrontal cortex (Duncan and Owen, 2000), but has yet to be explicitly studied across a range of cognitive processes within the FP. To further investigate the task-based functional connectivity of the FP, we conducted co-activation based parcellation (Eickhoff et al., 2011; Johansen-Berg et al., 2004) in conjunction with MACM. This allowed us to test whether regional differences in the whole-brain functional co-activation patterns of the FP enable identification of discrete subdivisions of the region. These frontopolar sub-regions were then functionally characterized by means of forward and reverse inference to determine their behavioral profiles according to the BrainMap taxonomic classification system.

## Methods

### *Region of interest definition*

The region of interest (ROI) for each hemisphere encompassed the two cytoarchitectonic areas of BA 10; the lateral frontopolar area 1 (FP1) and the medial frontopolar area 2 (FP2) as defined by Bludau et al. (2014). A detailed description of the analyses carried out to identify the cytoarchitectonic organization of the FP can be found in Bludau et al. (2014). In summary, observer-independent detection of cytoarchitectonic borders was performed via histological analysis of 10 post-mortem human brains. To this end, histological sections (thickness = 20 μm) containing the frontal polar region were digitized with an in-plane resolution of 1.02 μm per pixel. Gray-level index (GLI; Wree et al., 1982) images of these slices were then calculated, thus providing a means for identification of the cytoarchitectonic organization for the region (e.g. identification of the borders for each cellular layer within the cortex, volume fraction of cells within cellular layers). A sliding window procedure was used for border detection along the cortical ribbon, which compared adjacent groups of profiles against each other (Schleicher and Zilles, 1990; Schleicher et al., 1999, 2000, 2005, 2009).

The frontopolar areas were 3D-reconstructed using linear and non-linear transformation algorithms (Hömke, 2006), and normalized to the T1-weighted single-subject template of the MNI (Montreal Neurological Institute; Evans et al., 2012; Evans et al., 1992). From there, a Q16 maximum probability map (MPM) of Fp1 and Fp2 was created that assigned the cytoarchitectonic area of each voxel with the highest probability in the reference space of the MNI template (Amunts et al., 2005; Eickhoff et al., 2005, 2006). This allowed the inclusion of only those voxels into the ROI where the frontal polar fields had been more likely found than any other brain region in histological examination (Fig. 1A).

Taking into consideration that the FP includes a midline region along the medial wall of the rostral frontal lobe, we separated the initial search region into two independent ROIs for the right and left hemispheres. This was done to ensure that resultant parcellation solutions would not contain cross-hemispheric clusters. The MPM of the right and left FPs was thresholded and reformatted into two binary masks, where Q17 voxels within the ROI were assigned a value of 1 and all other voxels a value of zero. The resultant left hemisphere ROI consisted of 3020 voxels, while the resultant right hemisphere ROI consisted of 2777 voxels (voxel size: $2 \times 2 \times 2$ mm$^3$) (Fig. 1B).

### *Data processing outline*

Once the boundaries of our ROIs (the right and left FPs) were established, a meta-analytic connectivity map was created for each voxel within each ROI. These voxel-wise MACMs assigned the probability of co-activation of each remaining voxel in the brain with the seed-voxel based on the thousands of experiments archived in the BrainMap database. Next, voxels within the ROI were grouped together (via k-means clustering) based on the similarities of their MACM co-activation maps. The stability and consistency of k-means cluster solutions were assessed using a combination of different cluster stability metrics to identify an optimal parcellation solution.

A second MACM was performed using each cluster within the optimal parcellation solution as independent seed regions. This step in our analysis yielded a whole-brain co-activation map for each cluster within the right and left FPs. Lastly, functional characterization of each cluster was assessed by testing for significant overrepresentation of taxonomic



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