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Identifying overlapping patterns of histological variation in the prefrontal cortex

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The prefrontal cortex (PFC) is cytoarchitecturally heterogenous. Portraying its organisation has challenged neuroanatomists for over a century (Brodmann, 1909). In particular, it is unclear how regional differences emerge from the patterns of specific cytoarchitectural features. We hypothesise a restricted set of large-scale axes can capture local differences in cytoarchitecture and help to explain the diversity of the PFC. Such investigations are now possible owing to BigBrain (Amunts et al., 2013), as well as the development of manifold learning approaches that enable low dimensional representations of complex datasets. We aimed to create a blueprint of cytoarchitectural differences in the PFC by applying an unsupervised manifold learning approach to BigBrain.

Method. We first defined the PFC using a gyral-based atlas projected onto BigBrain (Desikan et al., 2006; Paquola et al., 2021). We extracted staining intensity profiles across the entire PFC of BigBrain, depicting cell-body density by cortical depth. We calculated the correlation between staining intensity profiles across all points to assess inter-regional similarities. Then, we applied diffusion map embedding, a nonlinear dimensionality reduction approach, which produces a set of eigenvectors reflecting distinct histological axes (Paquola et al., 2019). Next, we calculated central moments (amplitude, mean, standard deviation, skewness, kurtosis) for each staining intensity profile and performed product-moment correlations between moments and eigenvectors to better understand what features may be represented by each eigenvector. Subsequently, we tested whether histological axes of the PFC follow spatial gradients. We manually delineated the precentral gyrus, the cingulate gyrus (middle and anterior sections) and the rectus gyrus. Then, we calculated the minimum geodesic distance from each vertex of the PFC to each reference. Finally, we used linear regression models to fit each eigenvector to the spatial gradients and evaluated the fit of increasingly complex models using Akaike information criterion (AIC) and R2.

Results. We found that 85% of the variance in BigBrain PFC histology could be captured by four large-scale histological axes (mathematically defined as "eigenvectors", E1=40%, E2=21%, E3=13%, E4=11%, Figure 1A). Each axis involves different patterns of cytoarchitectural variation, as determined by the staining intensity profiles. E1, the first axis, is highly related to the balance of the cellular density towards either upper or lower layers (mean and skewness) (Figure 1B-C). E2 was more sensitive to the cellular density in the most upper layer (standard deviation), and E3 relates to whether the cellular density is spread out or concentrated at a certain cortical depth (kurtosis). Moreover, we found that each large-scale axis was best explained by the interaction of our spatial references, indicating that the axes do not follow individual spatial gradients (Figure 1D-E). However, we found that the PFC was influenced by the spatial gradients differently along its histological axes.

Outlook. These histological axes help to contextualise similarities and differences between cortical areas. Future studies incorporating high field MRI and BigBrain2 could determine whether these large-scale patterns are identifiable across individuals. Defining large-scale structural patterns of the PFC may help to understand how complex functional dynamics propagate with respect to cytoarchitecture.

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