Interpreting predictions of cognition from simulated versus empirical resting state functional connectivity

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the neocortex. This brain region integrates a wide range of cortical and subcortical inputs and it is one of the first brain regions affected by Alzheimer´s disease. However, its synaptic organization in the human brain is largely unknown due to the difficulties involved in studying the human brain via electron microscope techniques. In the present study, we used Focused Ion Beam/Scanning Electron Microscopy (FIB/SEM) to perform a 3D analysis of the synapses in all layers of the medial EC from human brain autopsies with very short post-mortem delays. Using this technology, 12,974 synapses were fully 3D reconstructed at the ultrastructural level. We studied several synaptic parameters, including the synaptic density, 3D spatial distribution, the proportion of synaptic types (excitatory and inhibitory), as well as the size of each synaptic junction. Our results showed remarkable uniformity in the synaptic characteristics analyzed, regardless of the cortical layer: all layers had similar synaptic densities; most synapses were excitatory, displayed a random spatial distribution and were similar in size in all layers. Since the medial EC exhibits a complex cytoarchitecture and innervation, these results are rather surprising. Indeed, the present study constitutes the first extensive description of the synaptic organization of the neuropil of all layers of the EC, a crucial step to better understand the connectivity of this cortical region, in both health and disease. Future work will include additional synaptic parameters, such as the synaptic morphology and the identification of the post-synaptic targets, which would add critical information to determine the complete picture of the synaptic organization of the human entorhinal cortex at mesoscopic and ultrastructural levels.

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THE DISTRIBUTION OF NEUROGLIAFORM NEURONS ACROSS AREAS AND LAYERS OF THE PRIMATE CEREBRAL CORTEX

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We present the first complete map of the distribution of a class of neurons in the primate cortex: neurogliaform (NG) cells, a subclass of neurons expressing calbindin-D28K (CB+ neurons). This was achieved based on the combined use of AI-based image classification and computerized reconstructions, validated through the use of classical stereological techniques. This allowed the quantification of the density of NG cells across cortical areas and layers in 3 marmoset brains. NG neurons formed between 0.5% and 2.3% of the CB+ cell population in different areas. Even where most concentrated, NG cells only formed $<0.5\%$ of neuronal population. They formed a higher proportion of the CB+ population in areas involved in the planning and execution of action, including those forming the frontoparietal network. Auditory areas also tended to show relatively high densities of NG neurons. In visual cortex subdivisions of the dorsal stream tended to show relatively higher densities of NG neurons compared to ventral stream areas. The laminar distribution of NG neurons was distinct from that observed for other CB+ neurons. First, they were most densely concentrated at the level of layer 4 (or, in agranular areas, near the interface between layers 3 and 5). Second, outside layer 4 they were approximately as likely to be found in supragranular layers as in infragranular layers, depending on which area. In the dorsolateral prefrontal, orbitofrontal, medial prefrontal, ventral temporal and retrosplenial regions NG neurons tended to be more numerous in supragranular than infragranular layers, with the inverse being true for auditory, lateral/inferior temporal and insular cortical areas. These results demonstrate the feasibility of accurately mapping the entire distribution of neurochemically-defined cells across the entire primate cortex, and opens the way for a full characterization of other cell types based on the use of convolutional neuronal networks and computerized reconstructions.

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INTERPRETING PREDICTIONS OF COGNITION FROM SIMULATED VERSUS EMPIRICAL RESTING STATE FUNCTIONAL CONNECTIVITY

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The relation between structure and function of the brain, and how behavior arises from it, is a central topic of interest in neuroscience. This problem can be formulated in terms of Structural Connectivity (SC) and Functional Connectivity (FC), respectively representing anatomical connections and functional interactions between regions in the brain. Recently, a study by Sarwar and colleagues has demonstrated individualized prediction of FC from SC using machine learning, additionally showing that variation in cognitive performance is explained by simulated FC (sFC) almost as well as by empirical FC (eFC). We investigated how decisions made to predict cognition differ between the models based on eFC and sFC. We predicted cognitive performance with Lasso regression in 100 cross-validation loops from both eFC and sFC separately, using FC between each of the 2278 pairs of regions in the 68-region Desikan-Killiany parcellation as features. We identified relevant predictors of cognition by inspecting permutation importance scores and keeping only features whose importance scores were consistently high across validation loops. 13 eFC features and 21 sFC features survived this procedure. Of these, only one feature overlapped between eFC and sFC. Analyzing overlap between regions corresponding to important features and functional systems known to support cognition revealed no patterns for either eFC or sFC features. In conclusion, we found that while cognition can be predicted from sFC almost as well as from eFC, different features are used in the models, and these features were not found to follow any structure in terms of functional systems. This shows that while machine learning models provide a theoretical upper bound on how accurately function can be predicted from structure, they do not necessarily produce output that can be interpreted in the same way as the data the models were trained on.

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