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Mapping neurotransmitter receptor distributions in the macaque cortex

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Introduction: Quantitative maps of neurotransmitter receptor densities are important for characterizing the brain's molecular organization. We previously presented a 3D reconstruction pipeline for 2D autoradiographs to create 3D atlases at up to 50μm resolution [1]. Here, we use 3D reconstruction of autoradiographs from a macaque hemisphere to investigate patterns of receptor distribution and the balance of inhibitory, excitatory, and modulatory neurotransmitter receptors.
Methods: Four hemispheres (3 left, 1 right) from the brains of 3 adult male Macaca fascicularis were serially sectioned and visualized for 15 different neurotransmitter receptor binding sites using quantitative in vitro receptor autoradiography [2-3]. The 2D sections were reconstructed into 3D using our previously described BrainBuilder pipeline [1]. As no MRI was acquired for the macaque brains, the MEBRAINS template brain [4] was used as the reference volume to which the autoradiographs were reconstructed with our pipeline (Fig.1A). The 3D volumes were reconstructed at 0.5mm resolution for inhibitory (GABAA, GABAB), excitatory (AMPA, NMDA, Kainate), and modulatory (5-HT1A, 5HT2, M1, M2, M2, α1) receptors. Reconstructed volumes were flipped over the midline of the coronal plane and averaged together. Receptor densities were then projected onto the MEBRAINS surfaces and normalized by z-score. Vertex-wise gradients were calculated using 14 reconstructed receptor maps with principal component analysis and Pearson correlation. The ratios of excitatory glutamatergic to inhibitory GABA (E/I) receptors were calculated as well as the standard deviation and entropy of receptor densities. To identify unique receptor distribution patterns, each receptor was regressed onto the other receptor distributions with Elastic-Net, and the entropy of each receptor distribution was calculated over the cortex.
Results Fourteen 3D receptor maps were reconstructed (Fig.1B), and the first three principal components explained 49%, 14%, and 10% of the variance, respectively (Fig.1.C). The 1st gradient component highlights the visual cortex and segregates it from cortical areas associated with the default mode network and association cortices. This sensory-association axis was also reflected in the E/I ratio and measures of variance (standard deviation and entropy). The uniqueness of the receptor maps was characterized by calculating the linear dependence and entropy of the receptor maps, revealing a cluster of unique receptors: Muscarinic M2, 5-HT1A, α2, GABAA Benz., Adenosine 1 (Fig.1D).
Conclusion: We demonstrate gradients of receptor distribution across the macaque cortex with a particularly strong axis separating the visual cortex from the precuneus and posterior parietal cortex, both part of the default mode network [5]. The visual cortex presents a conspicuously low E/I ratio and high variability in receptor distributions. The 2D autoradiograph sections were reconstructed to 0.5mm resolution to provide gross anatomical information. The data supports reconstruction up to 50μm resolution. We will investigate microscale patterns of receptor distributions to elucidate the molecular architecture of the macaque brain at a previously inaccessible resolution.

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