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Personalized Human Brain Energy Atlas: Machine learning-based neuropil density from anatomical MRI

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Neuropil represents the fundamental unit in which cellular signals are processed, and it consists of neuronal/glial cells whose finest filaments form synapses. Thus, neuropil density (NP) combines both cellular (i.e., neuronal/glial cells) and synaptic masses and is central to understanding the heterogeneity of brain metabolism. Current bottom-up energy atlases use NP-derived neuronal (NeuDen) and synaptic (SynDen) density maps. However, a great innovation would be to predict metabolism from personalized neuroanatomy.

We hypothesize that in vivo NeuDen and SynDen can be derived from longitudinal relaxation time weighted MRI (T1w) for gray/white matter distinction and diffusion MRI for tissue cellularity (apparent diffusion coefficient, ADC) and axon directionality (fractional anisotropy, FA). We present a proof-of-concept machine learning algorithm that successfully predicts NeuDen and SynDen from routine in vivo MRI scans, where ex vivo Merker stain (BigBrain) and in vivo SV2A-PET imaging were respective gold standards. Our machine learning algorithm used gaussian-smoothed T1w/ADC/FA on a voxel-by-voxel basis to predict NeuDen/SynDen maps. We trained and compared NP predictions to NP gold standards and used histogram/spatial correlations as a proxy for prediction efficacy.

Notably, training on group average MRI data, especially with high gaussian smoothing, was ineffective for NP predictions. We used different levels of isotropic gaussian smoothing to provide our neural network nondirectional neighborhood information. Providing only low levels of gaussian smoothed datasets resulted in grainy neuropil predictions, showing the importance of neighborhood information from highly smoothed input datasets. Neighborhood information also helps to mitigate SNR issues (by averaging out the noise) and minor misregistration errors. Additionally, smoothed datasets can also provide a regional baseline to calculate relative changes in T1w, ADC and FA by the neural network as needed for neuropil prediction. High subject-by-subject histogram correlations for SynDen (0.94) and NeuDen (0.88) demonstrated realistic estimates across all subjects, while lower spatial correlations illustrated individualized predictions for SynDen (0.85) and NeuDen (0.45).

In summary, NP represents the microscopic infrastructure that regulates function which can be measured at the mesoscopic level (i.e., millimeter sized voxels in the human brain) with various PET and MRI methods. Since decreases in NP are associated with disorders such as depression, Parkinson's, Alzheimer's and aging, this work paves the way for individualized mesoscopic energy atlas prediction, enabling microscopic interpretations of functional neuroimaging data across health and disease.

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