Functional and Molecular Imaging of the Serotonin System in the Human Brain

PhD thesis defence by Vincent Beliveau MSc
Tuesday, February 27th 2018 at 3 pm
Rigshospitalet, Auditorium 93
After the defence, the Neuroscience Center will host a reception at the Neurobiology Research Unit, Rigshospitalet, Juliane Maries Vej 28, 3rd floor

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Summary

The serotonin (5-HT) system plays a central role in the regulation of brain function and its disruption and/or imbalance has been linked to many brain disorders. Although the 5-HT system has been extensively studied in animal models and post-mortem tissue, many facets of the 5-HT system in the in vivo human brain remain to be fully characterized. In the work presented in this thesis we sought to investigate the functional connectivity and the spatial structure of the 5-HT system by taking advantage of the unique high resolution PET, MRI and fMRI data available in the Cimbi database.

The raphe nuclei form the seat of the serotonergic projections throughout the mammalian brain. Hence, they are an ideal proxy for identifying brain function linked to the 5-HT system. We investigated the functional connectivity of the 5-HT system by finding which brain regions were synchronized with the activity of the raphe nuclei in the human brain at rest, as measured with resting-state functional MRI. In order to assess if the strength of the synchronization is related to a feature of the 5-HT system, we subsequently investigated the extent to which it was associated with corresponding serotonin transporter density.

A detailed in vivo mapping of the 5-HT system in the human brain offers the opportunity to investigate the spatial characterization of the 5-HT system. Taking advantage of the high resolution PET images of the Cimbi database and the availability of corresponding structural MRI, we created an in vivo 5-HT atlas of the human brain receptors 5-HT_{1A}R, 5-HT_{1B}R, 5-HT_{2A}R and 5-HT_{4}R and the transporter, 5-HTT. We validated this 5-HT atlas by comparing it to measurements from autoradiography studies, which in turn also allowed us to convert the PET measures into densities. The spatial association between density and levels of genetic information was subsequently investigated using data from the Allen Human Brain Atlas.

Brain parcellations derived from features such as cytoarchitectonic boundaries or functional activation may not represent a correct representation of the underlying distribution of the 5-HT receptors and transporter. Hence, creating a new parcellation specific to the 5-HT receptors and the transporter can provide a model more relevant to the 5-HT system than existing ones. Changes in the dynamic profile of PET data reflect changes in receptor density and may contain important characteristics to segregate brain regions based on variation of the receptor distribution profile. We derived and implemented two probabilistic parallel factor analysis models to identify, from the dynamic PET data, brain regions with distinct dynamic properties. These models take advantage of common modes in the data (e.g. space and time) to identify latent components summarizing the data across another mode (e.g. subjects). The models were validated through simulation, applied to the dynamic PET data and additionally to an fMRI dataset to test its applicability to other modalities.