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Quantitative evaluation of peptide analogue distribution in mouse tissue using 3D computer modelling

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Introduction

For the individual the consequence of obesity includes an increased risk of acquiring metabolic diseases like type 2 diabetes and also cardiovascular disease [1]; Developing drugs for treatment of obesity has long been in focus for many in the pharmaceutical industry, but so far very few companies have been successful. For drugs to work in the brain they have to cross the blood brain barrier. One technique to investigate blood brain barrier crossing is *Light Sheet Fluorescence Microscopy* (LSFM) imaging which is a non-destructive method to produce well-registered optical sections suitable for 3D reconstruction [2]. The use and public availability of computational atlases is increasing in neuro-imaging employing various imaging modalities both in humans and animal models [3,4]. Atlas-based methods provide full brain segmentations usually at high computational cost. If a limited number of brain structures are of interest and they exhibit adequate contrast in the images, shape models capturing the shape variability of these structures may be applied [5].

Project idea and objective

In brief the aim is to build a computational atlas based segmentation algorithm and software that will:

- Allow segmentation of important appetite regulating centres in the brain
- Allow automated quantification of fluorescent signal in the brain
- Quantify the differences observed between the distribution of different GLP-1 analogues
- Test for differences between various physiological states such as fasted/fed, sleep/awake and different obesity models

If successful, this PhD will provide a much needed tool for developing the obesity drugs for tomorrow.

References

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4. Lein ES et al., “Genome-wide atlas of gene expression in the adult mouse brain”, Nature 445:168-176, 2007
5. T.F. Cootes et. al., "Robust and Accurate Shape Model Fitting using Random Forest Regression Voting", ECCV 2012
6. J. L. Lancaster et al., “Automated Talairach Atlas Labels For Functional Brain Mapping”, Human Brain Mapping, Vol. 10, 2000
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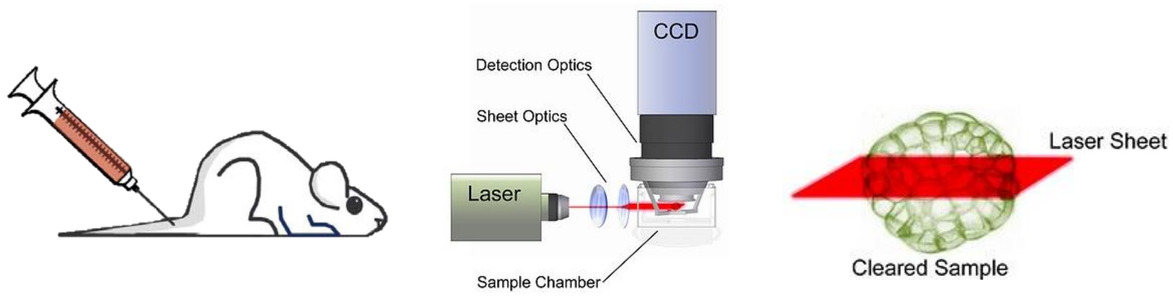
Methods

Animal studies and laboratory work

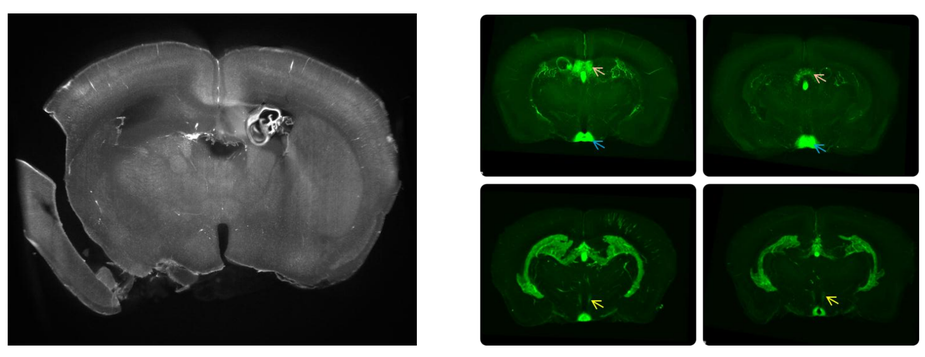
Fluorescent bound peptides are injected into a mouse following a waiting period of 6 hours to allow the peptides to cross the blood brain barrier and distribute inside the brain. The animal is euthanized and the brain is removed and cleared by a chemical process. The brain is scanned by LSFM using two different wavelengths: One setting to excite the tissue by auto-fluorescence (anatomical) and another setting to excite the fluorescent bound peptides (functional).



Work flow showing the laboratory work including injection of fluorescent bound peptides into the animal model, and scanning the chemically cleared brain using LSMF.

Image analysis

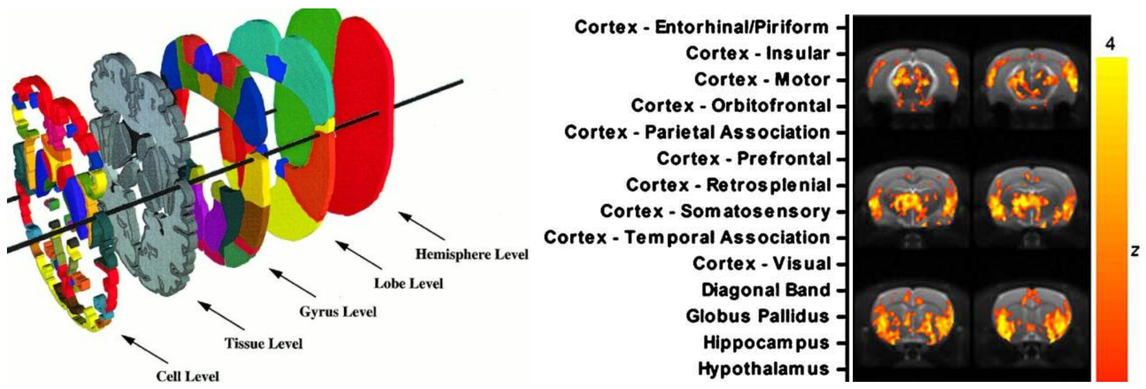
A brain atlas is build by manually annotating the anatomical part of a representative number of brain scans and building a registration algorithm to spatially align these scans. Future brain scans will then be analysed by image registration to the atlas (average image) and superimposition of the segmented structures from the atlas.



Left: Example of anatomical part of a LSFM scan. Note the damage of the tissue caused by the chemical clearing. Right: Example of the functional part of a LSFM scan. The fluorescent labelled peptides have bound to specific brain structures,

Quantitative measures

Quantification of the fluorescence signal is performed inside the segmented brain regions. Difference is expected based on peptide formulation, physiological states and animal model. The quantification will be based on different distance measures to investigate the crossing of the blood brain barrier.



Left: Example of a framework for brain segmentation using different scales [6]. Right: Example of quantification inside segmented regions [7].

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