Mass Spectrometry for Multimodal Imaging of Lipids in Brain Tissue

6.4. Valorisation

The brain is the control organ of our bodies and the desire to understand its organization and functioning is as old as mankind. A number of ongoing international brain research projects, such as *The Human Brain Project* [245], *The Allen Brain Atlas* [196] or *The BRAIN Initiative* [246], prove that brain research has been receiving particular attention in the past decade. These ambitious projects are focused on elucidating how the brain functions and "how it enables the human body to record, process, utilize, store, and retrieve information" [246]. They also target pathological states of the brain and are "seeking new ways of treating, curing, and even preventing brain disorders." [246] Maladies such as neurodegenerative diseases, mental disorders and stroke are, indeed, of great clinical importance. Many of these disorders are currently incurable. As such, they have a great impact not only on the quality of life of the patients and their families but also represent a significant economic burden for the society [29].

The brain's biochemical processes are dependent on mutual interactions and spatiotemporal translocations of molecules [5, 64]. Various chemical entities are also known to be involved in some brain disorders including depression (decrease of serotonin), Parkinson's disease (decrease of dopamine), Alzheimer's disease (decrease of acetylcholine and accumulation of excitatory amino acids such as glutamic acid, GABA, aspartic acid and glycin) or schizophrenia (increase of dopamine). Hence, in order to better understand the brain and the processes underlying its pathological states, it is imperative to gain more knowledge of the brain at the molecular level.

To this date, various analytical methods have been developed to study the molecular composition of the brain. Among them, *molecular neuroimaging* has the unique capability of providing simultaneous information on the *identity and position* of molecules within the brain. The major challenge in molecular neuroimaging is to achieve high molecular specificity at high spatial resolution. Mass spectrometry imaging (MSI) is a relatively young molecular imaging technique which addresses both of these aspects with a particular success.

In this thesis, I presented MSI as a powerful technique to study the brain at the molecular level, with the emphasis on lipids. Brain and the central nervous system (CNS) are extremely rich in lipids, which play structural roles and also participate in many biochemical processes of the CNS [29]. On one hand, changes in lipid metabolism can significantly influence brain function (for example, the case in lysosomal storage disorders such as Niemann-Pick disease [24]). On the other hand, many brain pathologies have been shown to be accompanied by qualitative, quantitative or spatial alterations of the lipids within the brain [25, 28]. For example,

links between lipids and the pathological mechanism of several neurodegenerative disorders have been described: It was shown that cholesterol contributes to the formation of amyloid plaques in the brains of Alzheimer's disease patients [25] and the same role was attributed to docosahexaenoic acid during Parkinson's disease [247].

Owing to its high molecular specificity and relatively high spatial resolution, MSI allows us to study the brain lipidome in a great detail. For example, MSI was employed to study not only cholesterol distribution [45, 60] but also global phospholipid changes [59] in the brains of Alzheimer's disease patients and transgenic mouse models of the disease. Results of these studies confirm the role of MSI as a powerful tool for the investigation of brain's lipidome (and its entire "moleculome").

Constant improvement in methodology is essential in all scientific fields, including mass spectrometry (imaging). In this thesis I described novel methods for MSI of lipids in the brain tissue. The protocols improved both, the qualitative and the spatial aspects of MSI. Moreover, they led to a proposal of a comprehensive workflow that can be applied in further molecular investigation of the brain and partly other tissue types. This suggested workflow can ultimately contribute to the molecular understanding of the brain and to monitor lipidome alterations related to its pathological states.

The work presented in this thesis is of interest to researchers working in biomedical fields, including neuroscientists involved in research of the molecular pathology of brain disorders, such as Alzheimer's disease or neuropsychiatric disorders. MSI can complement analytical methodologies routinely employed in neuroresearch. Thus, it can offer a deeper understanding of the changes in the molecular organization of the brain caused by its pathological states. Furthermore, researchers involved in the investigation of lipids and mass spectrometry (imaging) will also benefit from the new protocols described herein. The work reported in this thesis includes collaborative studies involving research groups specialized in different fields of science. These include groups devoted to instrumentation development, software development (image co-registration) and the study of lipid metabolism disorders. By linking a broad range of expertise, this thesis presents novel analytical approaches and the software capability to deliver practical and powerful analytical tools.