Laminar fMRI at ultra-high fields

Valorisation

The work presented in this thesis describes important methodological developments that are not directly *valorisable* (making knowledge available for economic and/or societal use) but are of value to scientists pursuing basic research and methods developers. The work presented here can be seen as building blocks for applications that can create wider societal and economic impact. These applications will also stand to benefit from the recent adoption of ultra-high field MRI (7 T) into the clinical environment. Under these caveats, the valorisable aspects of the work presented in the thesis are described in this addendum.

Over the past couple of decades, Magnetic Resonance Imaging (MRI) technology has permeated the societal landscape having had enormous impact in the progress of diagnostic healthcare and modern medicine. MRI has achieved mainstream adoption being the tool of choice for imaging the internal structures of the human body such as the soft tissue, blood vessels, etc. in health and disease. In the neurosciences, however, neurological or psychiatric conditions (such as pain, depression etc.) are not easily associated with readily visible structural abnormalities (such as tumours, lesions etc.). One way to address this is to use methods that allow detection of brain function. Until the early 1990s, the only way to achieve mapping of brain function was using radiolabelled tracer molecules that can respond to changes in blood flow or glucose consumption, and measuring these changes using positron emission tomography (PET) or single photon emission computed tomography (SPECT). MRI-based functional mapping, on the other hand, is non-invasive and is considered to be a safe technology due to the absence of ionising

radiation and radioactive tracers.

Functional MRI (fMRI) typically uses an intrinsic contrast mechanism that is sensitive to local changes in blood-oxygenation (blood oxygenation level dependent, BOLD) during brain activity, proving a rapid and safe method to assess brain function. While the early fMRI efforts were focussed on mapping different brain areas ("functional corticography"), the availability of ultra-high field MRI systems ($\geq$ 7 T) has ushered in a new era for functional neuroimaging in humans enabling fast, high-resolution, acquisitions that permit precise localisation and allow mapping of sub-areas of the brain. Despite all the advances in ultra-high field, high-resolution fMRI research and technology, fMRI has not taken the clinic by storm, making it difficult to "valorise" in the sense of direct commercial or industrial impact. Nevertheless, there is no doubt that MRI is *the* tool that could shed more light on different aspects of living human brain and pave the way to clinical treatments. The potential usefulness of fMRI for clinical populations has been best described in a fantastic blogpost by Prof. Dr. Peter Bandettini[1]. Among the issues raised for the lack of clinical adoption is that fMRI requires several intermediate data processing steps to become interpretable (this is true at all field strengths). At ultra-high field, the complexity of these strategies is compounded by the sheer size of the data being acquired, resulting in increased computational time and requiring computational, data analysis expertise that often falling outside the purview of even a trained Radiologist. Therefore, effective data processing and analysis strategies could turn the tide for potential clinical applications of fMRI. Specifically, the work presented in this thesis describe novel data acquisition, processing and analysis strategies for high-resolution fMRI targeted towards investigating the mesoscale (0.5-1.0 mm) architecture of the human brain

[1] BrainBlog: If, how, and when fMRI goes clinical

and therefore, has an inherent "value" to field beyond the application to laminar fMRI.

While many existing MRI tools are optimised for whole-brain datasets, higher spatial resolution data often only cover a region of the brain one is investigating. The work presented in this thesis presents approaches and algorithms that can be used to deal with partial coverage (f)MRI data. A stumbling block in MRI research is the making novel MRI sequences across sites and vendors. There are several MRI vendors, e.g. Philips, Siemens, but work with different software ecosystems for programming the techniques. For example, **Chapter 2** of this thesis emphasises the value of acquiring anatomical data that are distortion-matched to the functional data. Adoption of this approach is currently only limited by the fact that different ultra-high field scanners are operating on different software versions requiring considerable reprogramming of the sequence. This is notwithstanding the fact that the underlying physics is the same. The distortion-matched anatomical acquisition scheme used in the **Chapter 2** was recently programmed in a Philips environment by van der Zwaag and colleagues. Hopefully, this will be easier in the near future thanks to recent progrses in open-source pulse sequence development frameworks such as *Pulseq*[2]. The open-source frameworks allow the programming of MRI pulse sequences outside the vendor-controlled environment and with little effort by sequence programmer, prepares them to be executed on any scanner.

The laminar fMRI acquisition strategy presented in **Chapter 3** was inspired by a technique in animal research called line-scanning fMRI [79] that allows both high spatial and temporal resolution for mapping laminar activity in a small patch of the cortex. While it may seem a niche application, the interest in line-scanning-

[2] `https://pulseq.github.io/`

like human laminar fMRI has since then increased with many sites successfully pickup the baton [275, 276]. Line-scanning-like fMRI in humans creates value in allowing us to investigate the cortical micro-circuitry in humans using 7 T MRI at nearly the resolution of the cortical layers themselves. There is further value in bridging the gap between invasive animal and non-invasive human research and possibly pave the way for research to be more translatable.

Other valorisable aspects are the technical and educational outcomes of the work presented in this thesis. There are algorithms and analyses packages freely available (such as FSL, SPM) that can be used for fMRI data processing. However, many of these tools have been developed to work with data acquired at field strengths of 3 T, typically for whole brain acquisitions at low spatial resolutions (2-3 mm). Given that the default parameters are sub-optimal for higher resolution 7 T data, the availability of the source code for these tools in the public domain has been absolutely critical in improving one's understanding of the algorithms and guide one's choices as to what parameters best suit the data they are working with. Furthermore, being an unabashed proponent of fair and open collaboration, the course of the present PhD has yielded active engagement with peers in the department and those at conferences sharing information without reservation. An example of this shared value, is an electronic poster presented at the annual meeting of the International Society for Magnetic Resonance in Medicine (ISMRM) 2018 [278]. Neuroimaging blogs `practicalfmri.blogspot.com` and `www.layerfmri.com` have been a great example of knowledge transfer and value sharing with respect to the practical aspects of fMRI research. An opportunity to contribute to the value sharing was afforded thanks to the author of `www.layerfmri.com` and has made it possible to describe some of the data processing strategies discussed in **Chapters 4-5**, in more practical detail than would possible

in a corresponding publication.

Lastly and arguably most importantly to some people, that the scripts and workflows developed over the course of the present work will be soon available online[3] as educational scripts (e.g. MATLAB LiveScript, R Markdown). In conclusion, it is important to underline the fact that the valorisation potential of even basic/fundamental research can be expanded by ensuring the knowledge generated is made available in an open and accessible way. Moreover, making the knowledge accessible can increase opportunities for collaboration and therefore, create value for the society through scientific progress, as a collective.

[3] Gitlab repository