Challenges and potential of 7T (f)MRI for investigating attention and perception

Valorisation

The practice of science may be restricted to certain groups of people, but the knowledge produced should belong to the public. The work presented in this thesis contains methodological development of atlas-based volumetry of the human nucleus basalis of Meynert (nbM) in neuroimaging studies, hypothesis testing on surface brightness perception in the early visual cortex using 7T fMRI, and experimental development of potential brightness illusion stimuli for future neuroimaging research. All of these efforts aim to answer some open questions in modern neuroscience. The findings may be mostly of interest to those members of the scientific community who share similar interests in the topic, and will have the most straightforward application for their own research. Individuals from the general public with a keen interest in the topics we cover may also be interested in our research, especially as the projects that are initiated in this thesis continue to develop in the future.

It has been well established that cellular loss of the nbM correlates with cognitive decline in dementing disorders such as Alzheimer's disease and is also a feature of Parkinson's disease. However, investigating the nbM with neuroimaging is challenging since the nbM is not visible in in vivo neuroimaging data due to the lack of MR contrast and its small size, therefore the definition of nbM in previous studies has heavily depended on an existing atlas. The accuracy of the definition of the region of interest (ROI) influences the accuracy of volumetric or functional measurements for the nbM. With an increasing number of neuroimaging studies focusing on structural changes of the nbM in patients and the functioning of the nbM in healthy groups, there is a pressing need to revisit the localisation of the nbM in these neuroimaging studies. In Chapter 2, we reviewed the human nbM ROI selection protocols used in recent MRI studies. We found a distinct lack of reporting nbM volume with meaningful physical units. Among studies

that did report the nbM volume with a physical unit, we found highly variable volume estimates. This variability could be due to the atlas used and the probabilistic threshold set, but also existed in studies using the same atlas and threshold. More importantly, we discovered that the accuracy of atlas-based volumetry is reduced when the atlas is applied to datasets with a much lower spatial resolution (1.3 mm isotropic and above). In addition to helping to interpret previous studies, this is especially critical information for future nbM (f)MRI studies, as the field moves towards higher resolution acquisition. It is then critical that researchers avoid analysis that converts high-resolution to much lower resolution, for example, 1.5 mm isotropic in standard MNI space from SPM DARTEL toolbox, 2/3 mm isotropic in functional space. While atlas-based methods have their limits, we have to acknowledge the fact that the nbM is still not visible in in vivo datasets despite the advancement of ultra-high field neuroimaging. By exploring ultra-high resolution post-mortem datasets, we showed that the nbM could be visualised on quantitative T_2^* dataset with 200 µm isotropic. To our knowledge, this is the first attempt to investigate which MR contrast would be beneficial to visualise this structure. This knowledge can be used in two ways: in the short-to-medium term it will be possible to build an nbM template based on ultra-high resolution post-mortem MR datasets to replace the existing nbM atlases created from a post-mortem T1 weighted dataset with close to 1.0 mm isotropic. Such an atlas could be especially relevant as the availability of submillimetre resolution (f)MRI (for which applying an atlas from lower resolution datasets is especially problematic) in daily research increases. In the longer term, with increasing advancement in MRI technology and techniques, it may eventually become possible to make individual in-vivo structural scans of the nbM for structural and functional investigations. Given the importance of the nbM in cognition, there will be future research focusing on its structure and function, on clinical application and on methods development for better study. Our efforts in Chapter 2 lay the groundwork and provide a potential vision for relevant studies in the future.

We next studied visual processes in the cortex, again using 7T fMRI. Our visual experience of the world is dominated by surfaces. However our understanding of the neuronal mechanisms of vision emphasises the processing of contrast edges. Exactly how our perception of surface interiors arises has been vigorously debated for over a century. In Chapter 3, we found a non-significant trend towards a positive early (corresponding to the positive-dominant BOLD averaged across 3 TRs) fMRI signals in the V1 representation of the probing region during luminance decrement of the inducer. In literature, there has been an ongoing debate about whether the early visual cortex participates in the processing of surface brightness. Although our results do not settle the debate, our efforts in Chapter 3 could be beneficial to future studies on the same topic. Our design was an adapted version from Van de ven et al. (2012) and was designed to be efficient in brightness induction and allow studying the cortical responses in each ROI for each luminance condition separately. Future investigations may consider using this, or a similar experimental design to uncover new information on cortical processing and the temporal response associated with surface processing. Meanwhile, we observed multiple temporal responses in different retinotopic regions for each luminance condition. This could imply different hemodynamic response function models in the region, which could suggest a different analysis procedure. We also suggest that future studies take the asymmetric responses of luminance increment and decrement into consideration. An effective method to balance the perception of the two luminance conditions is needed, for example, a staircase experiment could be arranged while the participant lies in the scanner before the experiment. Data quality is essential to the investigation of small cortical responses, such as the responses we observed in Chapter 3. In future studies, measures should be taken to improve the data quality. To reduce the effect of B1 inhomogeneity to data quality at 7T, one can use a dielectric pad during the acquisition or acquire SA2RAGE to correct the B1 map. Additionally, researchers should be aware of the asymmetric temporal signal-to-noise ratio (tSNR) between the two hemispheres for 7T fMRI experiments. Last but not least, our experience indicates that it would be wise to conduct a pilot experiment

with larger voxel size, either using 7T or 3T, to test the design before moving to the submillimetre resolution.

An additional avenue to explore in future investigations of surface perception is to use as powerful a stimulus as possible. To set up an experimental stimulus capable of inducing strong illusion for use in future investigations, in Chapter 4 we parametrically studied Anderson and Winawer' s textured stimulus and compared different testing methods using an online platform. The reason for using this stimulus is that it can produce dramatic illusions and allows a powerful control stimulus, generated by rotating the surround without changing the overall luminance. With the optimised stimulus, we discovered that the illusory perception can be induced by only varying the luminance of a small region of inducer near to the probing region' s border. Although the illusory effect from these experiments was small, and testing in the psychophysics laboratory will be necessary, it provides a new set up of stimuli that are potentially valuable for future behavioural and neuroimaging research. In our group there has already been an EEG study conducted using the stimulus developed in Chapter 4. It is a thrill to know that our work already inspires new research.

Although the findings from this thesis cannot be immediately translated into economic and practical applications, the process of scientific exploration could be intriguing to society. Nowadays, with the information explosion on the internet, we want to convey the message that the scientific community takes caution in the process of creating knowledge. Although each project has its own expectations, we did not let our expectations dominate the direction of our projects. Negative results can be personally upsetting, but the goal of the scientific endeavour is to pursue the objective truth and find new mysteries, rather than to force conclusions upon data that do not allow one to do so. Messages of caution, such as we give in our published work, are important in keeping the progress of science grounded in objective, observable phenomena. Thus, neuroimaging studies that suggest a shrinkage of the nbM associated with dementia

are in line with previous histological knowledge and appear valid, however the imaging methods used must themselves be valid for the work to add new knowledge. Furthermore, part of our projects studied the mechanisms of perception using illusory stimuli which produce a mismatch between the state of our perception and the actual sensory information. In addition to being interesting phenomena, these stimuli provide a powerful metaphor for a cautious approach to interpreting research findings. Thus, just as the brightness of two objectively identical surfaces may differ due to differences in the background, differences in the baseline during a neuroscience experiment can lead to apparently large differences between experimental conditions, even when none exist. Exciting research results, even and especially when they are in line with expectations, must therefore always be approached with scepticism and caution.

Finally, we are delighted to share our academic work with the scientific community and the public. This thesis and the work within has been or will be published in open access journals to facilitate accessibility to society. The publication is or will be accompanied by the release of analysis scripts and data that are necessary to perform the analysis. Projects have already been shared with research teams in Canada and France in order to promote science communication and collaboration. This may inspire future research and collaborations into the volumetry of subcortical structures and the neuronal mechanisms of surface perception.