A computational view of the brain plasticity at rest

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Chapter 8

Summary

The human brain at rest is characterised by the presence of spontaneous fluctuations in activity. Thorough understanding of the neuroanatomy and biological mechanisms underlying this intrinsic neural activity is still lacking. Such knowledge is key to interpreting observed behaviours in health and disease. Therefore, the overall goal of the studies presented in my thesis was to expand the knowledge on the biological and computational mechanisms underlying the plasticity of human brain activity at rest. In particular, I focused on the local interactions between visual cortical areas and how their connectivity/dysconnectivity may influence the global (network-wide) aspects of brain connectivity. A particularly useful tool for this type of study is resting-state functional magnetic resonance imaging (rs-fMRI), which enables researchers to record activity simultaneously throughout the brain during a relatively short time span. Moreover, it enables researchers to map the functional relationships across different brain areas in a non-invasive fashion and in the absence of stimulus-driven activity. Finally, rs-fMRI data acquisition requires very little effort from the participant. Together, this makes rs-fMRI a potentially powerful approach to investigate the consequences of neuro-ophthalmic diseases, even at their most advanced stage (e.g. near blindness in case of glaucoma). This is why rs-fMRI was used in the studies presented throughout this thesis.

My first objective was to build on the existing methods that can be used to study plasticity of the human visual cortex in health and in neuro-ophthalmic diseases (such as primary open angle glaucoma). One of these existing methods is connective field modelling (CF), which can be used to analyse rs-fMRI-based recordings of spontaneous neural activity using biologically-plausible models of cortico-cortical receptive fields. CF can therefore be used to characterise the cortico-cortical functional connectivity between visual brain areas. To improve on the conventional method, I implemented a novel, versatile framework for it, based on Bayesian statistics. This framework enabled me to estimate the underlying posterior distribution of each CF parameter and consequently, to quantify the associated uncertainty. I then used this Bayesian CF method to investigate whether it is possible to obtain meaningful CF estimates with 3T rs-fMRI data. The reason for using 3T rs-fMRI data was that this type of data is commonly acquired during clinical research. However, it is also characterised by a lower resolution and signal-to-noise ratio when compared to high-field fMRI data (such as 7T). To validate my new approach, I showed that the rs-fMRI-based Bayes CF approach can accurately reveal the visuotopic organisation of visual cortical areas by using 3T rs-fMRI data. Overall, I concluded that our novel Bayes CF framework provides reliable estimates of CF parameters and their associated uncertainties.

This led to my second objective: to investigate the cortical basis of an ophthalmic disease such as primary open angle glaucoma (POAG). To do so, next, I used the Bayesian

CF model to examine differences in the local functional connectivity between visual cortical areas in participants with primary open angle glaucoma (POAG) compared to age-matched controls. By using this approach, we showed that the CF in the early visual cortex of people with POAG are smaller on average compared to those in age-matched controls .

Finally, my third objective was to understand the functional processes behind visual misperceptions. For this, I also used rs-fMRI to investigate the functional processes underlying visual misperception symptoms, such as visual hallucinations (VH). To highlight the neural mechanisms contributing to VH, I am using a novel functional connectivity-based targeting approach to identify highly influential brain regions that are characterised by a high functional connectivity (referred to as “hubs”). The idea is that these hubs can serve as potential target sites for repetitive transcranial magnetic stimulation (rTMS) treatment. In one patient, after the stimulation intervention we recorded relevant changes in neural activity and reduced VH burden. Therefore, I concluded that my connectivity-based approach can be used to obtain objective evidence on the efficacy of rTMS treatment. Additionally, by combining rs-fMRI functional connectivity and graph theoretical approaches to capture the global and local aspects of connectivity, I investigated the neuronal basis of VH in another clinical condition: psychotic disorder (schizophrenia). In patients with psychosis, I found that widespread dysconnectivity within vision-related functional networks predisposes them to experience VH. Furthermore, a higher connectivity of the middle occipital gyrus compared to other brain areas may explain the relatively complex nature of psychotic VH.

My thesis thus demonstrates the fundamental and clinical relevance of measuring and examining fluctuations in spontaneous brain activity using rs-fMRI-based approaches. The new methods I developed in this thesis research will enable researchers to investigate the intrinsic functional connectivity at the local and global brain levels. Moreover, they will facilitate the clinical use of rs-fMRI at both initial and late stages of a disease. Therefore, my methods can help future studies to advance the understanding of functional connectivity of the healthy visual cortex as well as alterations thereof in pathological conditions. These novel approaches are key tools that will enable researchers to translate knowledge on how the brain works into the development of more refined diagnostic applications and therapeutic interventions.

Chapter 9

Samenvatting

Zelfs als het menselijk brein in rust is blijft de activiteit ervan spontaan veranderen. We weten nog maar heel weinig over de neuro-anatomische structuren en de biologische mechanismen die daarbij betrokken zijn. Dergelijke kennis is belangrijk voor het begrijpen van de menselijke waarneming en hersenveranderingen, zowel bij gezonde mensen als bij ziekte. Daarom was het algemene doel van mijn onderzoek het uitbreiden van onze kennis over de biologische en computationele mechanismen die ten grondslag liggen aan de plasticiteit van spontane menselijke hersenactiviteit. Daarbij richtte ik mijn onderzoek specifiek op het ontwikkelen van methodes om kleinschalige interacties tussen visuele hersengebieden, en grootschalige interacties op het niveau van hersennetwerken, te kunnen analyseren. Een veelgebruikt hulpmiddel voor hersenonderzoek bij mensen is functionele magnetische resonantie beeldvorming. Hiermee kunnen onderzoekers op een niet-invasieve manier en in een relatief korte tijd hersenactiviteit registreren, ook bij mensen die in rusttoestand zijn (rs-fMRI). Op basis van de gemeten activiteit kunnen de functionele relaties tussen verschillende hersengebieden in kaart worden gebracht zonder dat het nodig is om een stimulus aan te bieden. Een ander voordeel is dat rs-fMRI zeer weinig inspanning vereist van de deelnemer. Tesamen zorgt dit ervoor dat rs-fMRI zeer bruikbaar is om de gevolgen van neuro-oogheelkundige ziekten voor de hersenen te onderzoeken, zelfs in een vergevorderde stadium (bijvoorbeeld in geval van glaucoom bij bijna blindheid). Daarom richtte ik me in mijn proefschrift op het gebruik van rs-fMRI.

In mijn proefschrift toon ik de fundamentele en klinische relevantie aan van het meten van veranderingen in spontane hersenactiviteit met behulp van rs-fMRI. De nieuwe methoden die ik heb ontwikkeld maken het mogelijk om kleinschalige en grootschalige functionele verbindingen in de hersenen te onderzoeken. Bovendien maken ze het makkelijker om rs-fMRI klinisch toe te passen in zowel het beginstadium als tijdens latere stadia van een ziekte. Mijn methodes kunnen toekomstige studies helpen om het begrip over de functionele verbindingen van de gezonde visuele cortex en veranderingen daarin door ziektes te vergroten. Ze stellen onderzoekers in staat om hun kennis over de werking van de hersenen te vertalen naar nieuwe verfijnde diagnostische toepassingen en therapeutische interventies.