# A computational view of the brain plasticity at rest

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# Chapter 7

## Discussion

## 7.1 GENERAL DISCUSSION

The general aim of the studies presented in my thesis is to investigate the biological and computational mechanisms underlying the plasticity of the human brain by studying its activity at rest. To this end, I combined resting-state functional magnetic resonance (fMRI) recordings with biologically-plausible models to characterize the spatial and temporal organization of visual cortex in the healthy brain and to investigate which functional mechanisms are behind specific neurological conditions. Therefore, the first objective of the research presented in my thesis was to develop, implement and validate novel approaches that may help to expand our understanding of the human cortical circuitry at the local scale. I applied these to achieve my second and third objectives of this thesis: to investigate the cortical aspects of the ophthalmic disease primary open angle glaucoma and to understand the functional processes behind visual misperceptions. In the following sections, I contextualize their relevance for future research and the conditions that would allow their translation into clinical applications.

### 7.1.1 The Bayesian inference framework for connective field modelling

To overcome some of the intrinsic limitations of the standard connective field approach (CF, Haak et al. 2013), I presented and validated a Bayesian inference framework for the CF model. This approach provides several significant extensions to the standard CF model, one of which is the ability to compare different cortical receptive field models. In **Chapter 2** , the single circular Gaussian (SG) model used in the standard CF is compared with the Difference of Gaussian (DoG) model that can estimate the center-surround configuration of a population of neurons throughout the visual cortex. Our results showed that a simple Gaussian is preferred in a control population. Besides the DoG model, the Bayesian CF framework can be extended to other model definitions, i.e. elongated shape, oriented ellipse, polar Gaussian, and the Cartesian and Polar Log-Gaussian ( Zeidman et al. 2018; Kumano and Uka 2010). These models could possibly characterise additional properties of cortical interactions between visual areas or provide novel information on ophthalmic diseases (e.g. glaucoma).

Another novel aspect of the Bayes CF model is the estimation of the full posterior distribution for each CF parameter. In **Chapters 2** and **3**, we used this type of information to estimate the uncertainty that quantifies the variability and reliability associated with each of the CF parameters. In **Chapter 4**, we used it to quantify the reliability of data and quantify possible systematic bias between different groups. Aside from group comparisons, this distribution can be used to monitor the progression of a disease and/or the effect of an intervention at the single subject level. Finally, we introduced a novel and reliable data-driven threshold, based on the effect size of

the BOLD fluctuation (beta). This threshold is both voxel- and subject-specific, thus enabling both within-subject statistics and between-subject mixed effect analyses. Taken together, these features are expected to be especially useful when the Bayesian CF model is applied in a clinical population (e.g. a population with lesioned visual pathways or brain neurodegeneration); they can provide new insights into the underlying cortical mechanisms of neuro-ophthalmic disease, not only at the group level, but especially at the subject level.

Overall, the Bayesian CF framework presented here provides an improved and comprehensive tool to assess the neural properties of cortical visual processing that will help to further improve our understanding of the ongoing processes involved in perception, cognition, development, and ageing in both health and disease. I suggest the use of the Bayesian CF approach to study the following: i) brain adaptation and plasticity; ii) neurodevelopment and neuro-ophthalmic diseases; iii) single case studies (where it can be used to estimate differences at the voxel-level).

### 7.1.2 Properties of the visual cortex based on spontaneous brain activity

Based on the stimulus-agnostic and eye-movement-independent character of the CF model (Gravel et al. 2014; Haak et al. 2013), the Bayesian CF model characterises the intrinsic visuotopic organisation of the visual cortex even when applied to BOLD activity recorded in the absence of external stimulation (**Chapter 3**). In particular, the CF modelling at 3T provides qualitatively similar results to those previously observed at 7T, indicating that this lower but much more commonly available field strength is sufficient to characterise the brains of patients and individual cases. Therefore, this framework can be used to evaluate the quality of cortical processing in participants in which the visual input may be compromised by ocular or neurological lesions. It can also be used in blind participants.



### 7.1.3 Limited local reorganisation is present in adults with glaucoma

No two human brains are exactly alike, especially when referring to the brains of glaucoma patients. Every glaucoma patient has a unique visual field defect that might be reflected in specific and unique patterns of reorganisation at the brain level. In **Chapter 4** of this thesis, this reorganisation at the cortical level is evaluated based on shifts in the CF positions and sizes. Differences in the neuronal configuration of CFs are observed in the presence and absence of visual stimulation. Furthermore, these differences are not evoked by simulating scotoma in age-matching healthy participants.

Overall, I conclude that there is a limited degree of reorganisation in the primary visual cortex of adults affected by glaucoma, irrespective of the stage of the disease.

The discovery that glaucoma also has neurodegeneration or local reorganization characteristics has implications in the clinical setting. The potential involvement of the brain and its plastic mechanisms in this pathology suggest that the diagnosis should involve the assessment of neural functional changes and that the treatment strategy should consider the entire visual pathway. Our findings and those of others (Frezzotti et al. 2016; Chen et al. 2017; Cai et al. 2015), show that changes in the brain are present since early stage of the disease, fMRI should be considered as a complementary tool to evaluate the progression of glaucoma together with the quantification of neural changes, which might be used as a biomarker of this disease. Because fMRI is non-invasive and demands little from patients, it is a very compatible with the clinical setting albeit being more expensive than ophthalmic tests.

### 7.1.4 Resting state data as approach to define viable target brain areas

Another phenomenon that is characterised by the high inter-subject variability is the occurrence of visual hallucinations. In **Chapter 5** of this thesis, a novel connectivity-based targeting approach is presented. Based on rs-fMRI data combined with an eigenvector centrality method (ECM,Wink 2019; Wink et al. 2012), this novel approach enabled us to identify regions of high-connectivity ("hubs") within functional brain networks at the subject level. In a case study, these hubs were identified as viable target sites for rTMS treatment. Subsequently, the same connectivity-based approach was used to monitor the effect of the intervention (noninvasive brain stimulation). Similar to **Chapter 3** and **4**, the posterior surrogate distribution was used to make a comparison to account for scan-to-scan variability.

The self-reported decrease in VH intensity was accompanied by the selective change in ECM values of the identified target area (SMA) and the hippocampal area. This could indicate a potential functional explanation for the reported decrease in VH.



In **Chapter 6**, we extended this connectivity-based approach to another clinical condition: psychotic disorder (schizophrenia). Focusing on the group level, we found that widespread dysconnectivity within visual-related functional networks predisposes patients with psychosis to experience VH. Inadequate co-functioning and switching between the Default Mode Network and Dorsal Attention Network, possibly due to impaired Salience Network functioning, may lead to attributing the wrong origin to visual percept, thus resulting in a visual hallucination. Furthermore, the middle occipital gyrus appears to be characterised by a high centrality compared to other brain areas in the visual network. This is probably related to the complex nature of psychotic visual hallucinations. Such understanding is relevant, particularly because local network integrity may affect the applicability of future treatment and rehabilitation. Therefore, it is critical to understand the relationship between the integrity of patients' functional

networks and their visual field loss and develop methods to quantify this relationship.

All together, these results show how rs-fMRI data in combination with an accurate connectivity-based approach can serve as a tool not only to guide and monitor an intervention in clinical applications, but also to study the underlying brain mechanisms at an individual and at the group level.

## 7.2 FUTURE DIRECTIONS AND CLINICAL APPLICATIONS

In this thesis, I have presented two novel approaches to investigate the role of spontaneous neural activity plasticity as indexed by functional connectivity in health and disease. These models can also enable advances in our understanding of mechanisms that govern the function of the brain in general. Below, I discuss possible potential approaches to improve this understanding.

### 7.2.1 The dynamic's aspect and neuroanatomical basis of rs-fMRI signal

Focusing on the local organisation of the visual cortex, the CF model enables mapping of cortico-cortical population receptive fields at rest. These CF maps still show a retinotopic organisation that resample the organisation activated by stimulus-driven data. This result indicates that the CF model reflects the underlying neuroanatomical organisation and the key role it plays in shaping the functional interaction between cortical areas. An important improvement of this Bayesian CF model would be to combine it with some neuroanatomical information as a way to estimate the CF properties. Future studies could use properties of the visual cortex (e.g. cortical magnification factor, receptive field size) or anatomical parameters (e.g. fiber density, the myelination of the white matter) to define informative priors for the parameters of our model.

Such a cortico-cortical approach models brain connectivity as if it was represented by a constant state throughout the scan duration (Aedo-Jury et al. 2020; Menon and Krishnamurthy 2019; Liu et al. 2019). However, spontaneous BOLD fluctuations, even though they remain temporarily stable (2min-5min), are characterised by time-varying properties as a consequence of the underlying neural and metabolic activity. Therefore, future studies should also investigate the cortical correlations between brain areas in the temporal and spatial domain, thereby expanding the Bayesian CF model to capture additional, distinct dynamics in functional connectivity as well as their relationship with various cognitive and behavioral states in health and disease.

### 7.2.1 Resting-state fMRI: the power of a tailored approach in clinical application

Several studies presented in this thesis showed high inter-subject variability in the underlying mechanisms of neural activity in various neurological conditions. These results underlie a compelling need for improved detection and monitoring of the progression of these diseases and for estimating the efficacy of their therapeutic intervention even in single subjects. As we showed in **Chapter 5**, rs-fMRI data together with a reliable functional-connectivity based method provides a feasible approach that can be used in clinical practice. This connectivity-based approach is being used to assess local functional changes in primary open angle glaucoma (POAG) population. Little is still known about how these changes affect the integrity of the cortical functional networks at the global or local level. This approach may be beneficial to the low burden on the participants during data acquisition who are unable to undergo SAP due to their neuro-ophthalmic conditions, especially when they are at the most advanced stages (e.g glaucoma, blindness). Moreover, these approaches may greatly improve our understanding of the phenomenon of misperception (e.g. visual hallucinations) in the absence of external stimulation. Lastly, it can be flexibly combined with emerging treatments such as rTMS (**Chapter 5**) or more specific therapeutic interventions related to the visual system such as retinal or cortical implants to assess and monitor disease progression at different stages.

## 7.3 CONCLUSION

In summary, the studies presented in my thesis have demonstrated the importance of measuring and examining spontaneous BOLD fluctuations at rest using rs-based approaches to investigate the intrinsic functional connectivity at the local and global brain level in both health and disease applications. The novel techniques developed and presented in these studies represent important steps that can help future studies to more accurately characterize the functional connectivity of the visual cortex in healthy subjects as well as its alterations in pathological conditions at both initial and late stages of a disease. While my thesis focused primarily on resting-state fMRI signals recorded in the visual cortex, the approaches presented here can also be easily applied to investigate other sensory systems (i.e. auditory, somatosensory or motor cortical networks).

Overall, these novel approaches provide useful tools for advancing our knowledge on how the brain works, for translating this knowledge to clinical applications and for developing more refined therapeutic interventions.

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