A computational view of the brain plasticity at rest

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DOI:
10.33612/diss.183130118

Chapter 1

Introduction

In recent decades, functional magnetic resonance imaging (fMRI) has emerged as a popular, noninvasive technique that has been critical for advancing our understanding of the human brain functions in vivo. FMRI relies on the different magnetic susceptibility properties of oxygenated and deoxygenated hemoglobin (Linus Pauling 1936; Brindle et al. 1979; Thulborn et al. 1982). It measures low-frequency (< 1Hz) fluctuations of blood-oxygen level dependent (BOLD) signals of the brain in the presence or absence of external stimulation (Belliveau et al. 1991; Bandettini 2012; Ogawa 2012; Ogawa, Lee, Kay, et al. 1990) and it is usually represented by a Hemodynamic Response Function (HRF) that peaks at about 5 to 6 seconds after stimulus onset in the human brain (Bijsterbosch, Smith, and Beckmann 2017; Buckner et al. 1996).

Spontaneous (task-independent) BOLD fluctuations at rest have been widely used to investigate the intrinsic functional connectivity of the brain (Biswal et al. 1995; S. M. Smith 2012), and this approach is often referred to as resting-state fMRI (rs-fMRI or RS, Andreasen et al. 1995). In 1995, Biswal and colleagues were the first to observe the presence of bilateral spatial integration, coherent activity and functional connectivity between distant homotopic brain areas, even in absence of a task (Biswal et al. 1995). Several studies have replicated these findings, highlighting the key role of rs-fMRI to characterise the temporal and spatial patterns of interconnected brain regions (Cordes et al. 2000; Greicius et al. 2003; Gravel et al. 2014). More recently, numerous mathematical methods and biologically-plausible models have been implemented to estimate the statistical dependencies (as indexed by temporal correlations) between BOLD fluctuations across different areas of the brain (Figure 2). Such dependencies can be converted into connectivity matrices that represent the functional connectivity emerging from these regions (Smith 2012). However, the relationship between these correlations and their underlying neuroanatomy and biological mechanisms is still unclear. In particular, how these correlations relate to brain changes and possible adaptation (also known as brain plasticity) in response to certain neurological diseases remains a computational and biological challenge. The overall goal of the studies presented here was therefore to expand our knowledge of the biological and computational mechanisms underlying the plasticity of the human brain by studying its activity at rest. More specifically, I focused on the local interaction between visual cortical areas and how their connectivity/dysconnectivity may influence the global (network-wide) aspect of brain connectivity.

The first objective of the research presented in my thesis, therefore, was to develop, implement and validate novel approaches that may help to expand our understanding of the human cortical circuitry at the local scale. To do so, we used a Bayesian approach that enabled us to apply prior anatomical knowledge, define new parameters to more accurately estimate and control for the uncertainty associated with neural activity at rest.

A methodologically useful feature of a rs-fMRI approach in healthy and clinical population is the low burden it puts on the participants during data acquisition. Indeed, participants are commonly instructed to simply lay still in the scanner with their eyes closed, while allowing their mind to roam freely, i.e. not focusing their thoughts on anything in particular. This makes rs-fMRI a powerful tool to investigate patients with neuro-ophthalmic diseases (e.g. glaucoma), even at an advanced stage and in blindness, and to study the phenomenon of misperceptions (e.g. visual hallucinations) without external triggers. This leads to the second objective of this thesis: to investigate the cortical aspects of the ophthalmic disease primary open angle glaucoma.

However, few successful studies have been published on using rs-fMRI data towards application in clinical practice (Fox and Greicius 2010; Lee, Smyser, and Shimony 2013; Greicius et al. 2003). Clinical applications of rs-fMRI data require the implementation of reliable rs-fMRI analyses that can generate accurate conclusions at the level of a single participant. This brings me to the third and final objective of this thesis: to understand the functional processes behind visual misperceptions. In order to do so, I have implemented a tailored single-subject approach for identifying regions characterised by high connectivity and apply it to therapy-resistant visual hallucinations (VH) symptoms in a case study.

1. 1 THESIS OUTLINE

This thesis consists of five chapters based on experimental evidence. Chapters 2, 3, and 4 focus on the implementation and practical application of a Bayesian framework to investigate the cortico-cortical connections of the visual system in health and ophthalmic disease. Chapters 5 and 6 present our investigation into the cortical basis of visual misperceptions in which we combined whole-brain functional connectivity and graph-theory approaches. Chapter 7 consists of a discussion of findings, novel methodologies and their implication for our understanding of the brain plasticity. Below, I describe each chapter in more detail.

As part of the work presented in this thesis, I developed a novel Bayes framework, starting with the connective field (CF) modelling (Haak et al. 2013) reported in **Chapter 2**. By using a Markov Chain Monte Carlo (MCMC) approach, I translated the concept of standard CF modelling into terms of Bayesian inference. This enabled us to estimate the underlying posterior distribution of each CF parameter and then to quantify the associated uncertainty.

In **Chapter 3**, I tested the Bayesian CF approach and compared it to the standard CF

model when applied to rs-fMRI data (Gravel et al. 2014). Furthermore, I investigated whether it is possible to obtain meaningful CF estimates from 3T rs-fMRI data. These data are much more commonly used in clinical research but are also characterised by low resolution and signal-noise ratio when compared to high-field fMRI data (such as. 7T). Overall, I show that the novel Bayesian CF framework is a comprehensive tool that provides reliable parameter estimates when applied to task-based and rs-fMRI data.

In **Chapter 4**, I investigated the processes underlying functional reorganization of activity in the visual cortex following brain damage. Using advanced fMRI-based neural models (population receptive fields and Bayesian CF models), I examined changes in the local functional connectivity between visual cortical areas in participants with early to advanced stages of primary open angle glaucoma (POAG). I found limited differences in connective field properties in the early visual cortex of control participants and those with POAG.

The work presented in the last two experimental chapters (**Chapter 5 and 6**) of this thesis focused on investigating the neural underpinnings of visual misperception in a single participant and at the population level by taking a whole-brain connectivity approach. In **Chapter 5**, I developed a novel connectivity-based targeting approach to functionally identity brain regions showing high-connectivity (such a region is called a "hub"). The great potential of this single participant-based approach is its ability to identify areas that play a key role in pharmaco-therapy-resistant visual hallucinations. This feature enabled us to precisely target involved regions with rTMS. We used these identified regions as potential target sites for rTMS treatment in a single case study. This subject-based approach reduced the pharmaco-therapy-resistant visual hallucinations (VH) symptom of the patient. By using this approach, I was able to identify changes in the connectivity patterns, both in the target area and associated hubs involved in VH, thus indicating that this connectivity-based approach can be used to obtain objective evidence for the efficacy of rTMS treatment at the participant level.

Finally in **Chapter 6**, I investigated the neuronal basis of VH in patients with a psychotic disorder (schizophrenia). By combining functional connectivity and graph theory approaches, I found that a widespread dysconnectivity of visual-related functional networks predisposes patients with psychosis to experience VH. Moreover, high connectivity of the middle occipital gyrus compared to other brain areas was observed, which is likely to be associated with the complex nature of psychotic VH.

1.2 BACKGROUND

In the following sections, the anatomical organisation of a healthy visual system is briefly described. I also outline how neuro-ophthalmic disorders may alter its functionality, resulting in visual misperception of the world.

1.2.1 The visual cortical pathway: from eye to cortex

The visual processing of the external surroundings starts with the photoreceptor cells in the retina, rods and cones (Webb, Love, and Adler 2008; Gibson 2013; M. Gupta and Bordoni 2020). Cone cells enable the detection of colours, central vision and function only in bright light (photopic condition). Rod cells enable peripheral vision and function in low-light (scotopic condition). This asymmetry between cone and rod cells is gradual in the foveal and periphery. The central area of the retina, the macula, is specialised for high resolution vision. These photoreceptors are the site of transduction of external light (and therefore stimuli) in action potentials that are transmitted to the retinal ganglion cells (RGC) through complex local excitatory/inhibitory microcircuits. The axonal projection of RGC comprises the optic nerve, which transmits primarily to the lateral geniculate nucleus (LGN) through the optic chiasm. From the LGN, the visual information is propagated as action potentials through the optic tract, terminating in the primary visual cortex (Brodmann area 17) located on both sides of the calcarine sulcus. The cortical structures here follow a precise retinotopic ordering that is one of the main topics of this thesis.

Disruption at any level in this pathway results in visual field defects that might lead to misperception of the visual stimuli. Localising, interpreting and understanding them are crucial for an early diagnosis and to develop future treatments.

1.2.2 Retinotopic organisation of the visual cortex

From the retina, each optical nerve fiber carries information related to a specific subsection of the visual field and terminates in a precisely defined portion of the visual cortex (V1) (Hubel and Wiesel 2004; Livingstone and Hubel 1988). This is called retinotopic organisation and defines the information processed by each portion of the visual cortex (Reichl et al. 2012; Nauhaus and Nielsen 2014). Overall, more than 16 visual areas have been classified and their hierarchical organization has been shown (Wandell, Dumoulin, and Brewer 2007).

The primary visual cortex (V1), which is located along the calcarine sulcus and receives direct input from the LGN, is the first cortical region in the visual pathway where information from the two eyes is combined, resulting in an hemifield representation of the retinal image. Clustered together with V1, there are two other visual areas, V2

and V3, which are organised in dorsal and ventral visual streams (Wandell, Dumoulin, and Brewer 2007). This anatomical organisation results in a quarter hemifield representation of the retinal image. Many other visual cortical areas are organised similarly, reflecting that visual cortical areas preserve much of the level of organisation initially present at the level of the retina, where highly specialised receptors process different aspects of the visual input. In the first three experimental chapters of this thesis, I investigated possible task-dependent and task-independent changes in BOLD signals and determined how they related to the retinotopic organisation of the visual cortex in health and disease.

1.2.3 Primary Open Angle Glaucoma

Primary open angle glaucoma (POAG, hereafter referred to as glaucoma) is one of the most common causes of irreversible blindness worldwide. However, little is known about the exact pathogenesis of this disease (Quigley and Broman 2006; Flaxman et al. 2017; Chang and Goldberg 2012). A progressive loss of RGC, optic disc damage and retinal fibrous layer changes have been reported in POAG (Chang and Goldberg 2012). All together these factors cause a gradual loss in the visual field of view that typically is detected in the periphery. No cure is known, and current guidelines suggest therapies for lowering intraocular pressure (IOP), which is one of the most important and the only modifiable risk factor in POAG (Heijl et al. 2002). However in the last decade, evidence was found that damage not only occurs intraocularly, but also extends intracanically. In addition, the loss of RCG cells not only affects the optic nerve, but also the entire visual pathway (Chen et al. 2013; Wang et al. 2016). Therefore, glaucoma has started to be viewed as a neurodegenerative disease (Yücel and Gupta 2008; N. Gupta and Yücel 2007b; Nucci et al. 2013; N. Gupta and Yücel 2003, [a] 2007). Understanding how brain mechanisms might be affected at the functional level due to a prolonged lack of visual input could enable early diagnosis, and lead to the development of individually tailored therapies.

1.2.4 Visual misperceptions and hallucinations

Visual hallucinations (VH) are conscious visual perceptions (that occur while being awake) in the absence of an external stimulus. VHs are neuro-ophthalmological dysfunctions that are very disabling and are based on various pathologies, including eye disease, neurodegenerative disorders and psychosis (Manford and Andermann 1998; Waters et al. 2014; Shine et al. 2012; Teeple, Caplan, and Stern 2009). VHs comprise a range of different types of experiences from simple VHs, usually described as small, brightly coloured spots or shapes, to complex VHs like people, animals and landscapes (Teeple, Caplan, and Stern 2009). Complex VHs are the most common type of hallucination in psychotic disorders like schizophrenia. They also occur in Parkinson's disease (PD) (Shine et al. 2011; van Ommen et al. 2019). Besides being

very disabling in daily life, VHs are often treatment-resistant, but there is no clear explanation for their occurrence. Evidence was found that high-order visual areas together with dysfunction of neural processes are involved in the occurrence of these visual phenomena (Barrell et al. 2018; Shine et al. 2011; Bordier et al. 2018). The main aim of the final two chapters of this thesis is to improve our understanding of the neural basis of complex VHs in both schizophrenia and PD.

1.3 NEUROCOMPUTATIONAL MODELS

In the last part of the introduction, I provide a short overview of the functional connectivity approach and the graph theory measures used to investigate the neural network at the level of the whole brain. In parallel, I describe several biologically-grounded computational models used to characterise the cortical responses of the visual cortex.

1.3.1 Functional Magnetic Resonance Imaging (fMRI)

In order to record the neuronal population activity, fMRI uses a strong magnetic field to detect changes in the BOLD signal (Figure 1). This signal relies on the fact that hemoglobin has different properties according to its level of oxygenation which, in turn, fluctuates according to the level of activity of large clusters of neurons (Logothetis and Wandell 2004; Amaro and Barker 2006). By using the signal arising from these biological properties, fMRI can provide an indirect measure of neuronal activity. The activation of a cortical area causes an increase of oxygenated blood inflow higher than the necessary metabolic consumption. Changes in the blood ratio between oxyhemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic) can be detected due to their differential magnetic susceptibility and result in the recorded fMRI signal (Ogawa, Lee, Kay, et al. 1990; Ogawa, Lee, Nayak, et al. 1990). A limitation of fMRI techniques arises from their dependence on recording of such slow fluctuations in blood magnetization. Together with the sampling rate delay of MRI, this results in a sluggish signal characterised by low temporal resolution.

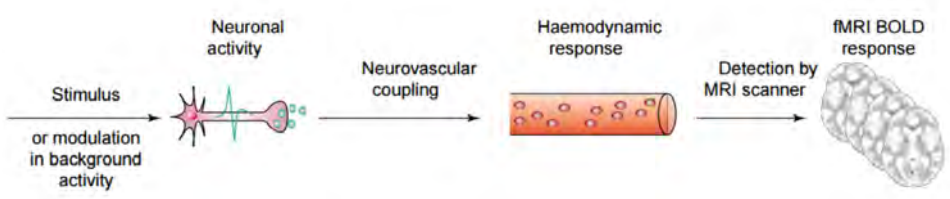

Figure 1 - The fMRI BOLD signal principles (Arthurs and Boniface 2002).

1.3.2 Functional Connectivity

Functional connectivity (FC) is traditionally defined as the statistical temporal dependencies in BOLD signal between anatomically separated brain regions and is interpreted as an index of their level of functional communication (Friston 2011; van den Heuvel and Hulshoff Pol 2010). When applied to rs-fMRI, the interpretation of this observed co-activations is challenging since an a priori hypothesis is absent due to the lack of a specific task. Numerous methods are available to compute FC on rs-fMRI (Figure 2). The most frequently used approaches are voxel-based or seed-based, data-driven (e.g. principal component analysis and independent component analysis), and network-based analyses. will focus on the latter ones since they were used in the work presented in the final two chapters of this thesis.

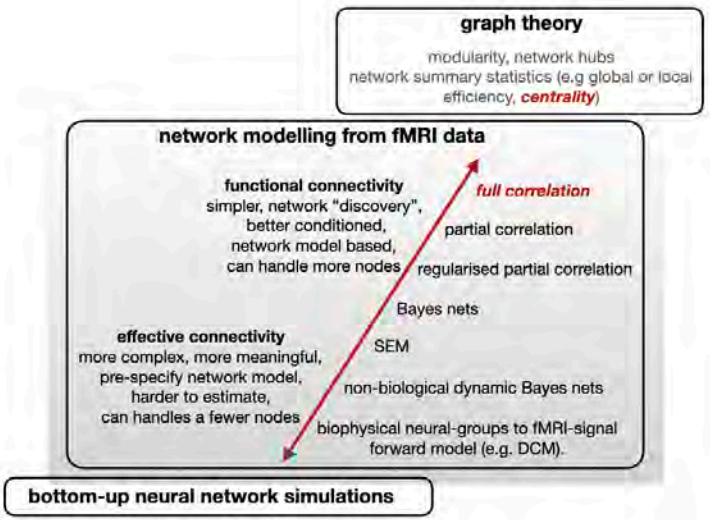

Figure 2 - Schematic of relationships between various network modelling analyses for/from fMRI (adapted from (S. M. Smith 2012). Methods used in these thesis are illustrated in red font.

Overall, the level of co-activation of spontaneous fMRI signals between different areas can be classified into modules and organised in networks (Smith et al. 2009), which are called Resting State Networks (RSNs). Each network is defined by a group of brain areas that are highly associated with specific functions such as vision, motion or hearing. These RSNs are consistent across healthy participants and show high correspondence to the networks emerging from task-based fMRI data (Damoiseaux et al. 2006; De Luca et al. 2006; Beckmann et al. 2005; Smith et al. 2009). Such network identification starts by identifying a set of "nodes" , i.e. spatially defined regions of interest (ROI), and then estimates the set of "edges" or connections between these nodes (Smith 2012).

There are many ways to define nodes. One of the most common, also used in this thesis, is to parcellate the brain on the basis of pre-defined anatomical or functional brain atlases (Eickhoff, Yeo, and Genon 2018). Once the nodes are defined, each is characterized by its own associated time-course (commonly the average time series from all voxels within that node). These averaged time-courses are then used to estimate the connections (edges) by computing correlations between nodes. This results in a node-to-node network matrix of all the edges, also called "graph". Once obtained, the graph provides a number of options for further node-based analysis. One of these methods is called eigenvector centrality mapping (ECM; Wink et al. 2012; Wink 2019; Lohmann et al. 2010; Joyce et al. 2010; Zuo et al. 2012). Based on the concept of centrality, ECM assigns a weight to each node that takes the following into account: i) the number of other nodes [C1] that this nodes is connected to and, ii) the importance of those connected nodes inside the network (e.g. direct connections to central ROI a given a higher weight since they are sharing more information). ECM thus identifies nodes or edges that play a central role in the functional network structure. This method has been used in **Chapter 5** to identify ROIs that might serve as target locations in rTMS treatment.

1.3.3 Retinotipic mapping of the visual cortex

In parallel to the growing number of methods to assess functional processes at the whole-brain level, many local, biologically-plausible models have also been developed. One approach of particular interest for the work in this thesis is the population receptive field (pRF) method (Dumoulin and Wandell 2008). By modelling the haemodynamic response of neuronal populations excited by a visual stimulus, pRF derives properties on the retinotopic organization of the human visual cortex (Engel et al. 1994; A. T. Smith et al. 2001). Briefly, the method is based on a visual stimulus, a haemodynamic response modelled by using a two-gamma HRF function (Boynton et al. 1996) and mathematical model of the neuronal population responses. In this thesis, a 2D symmetrical Gaussian kernel with width defined as sigma (σ), was used. To find the optimal pRF estimates, a set of predictions of the expected neural responses are generated by combining possible pRF models with the visual stimulus. These predictions are then convoluted with the HRF, resulting in a set of BOLD responses for each candidate pRF model. Finally, only the pRF parameters associated with an optimal fitting with the BOLD responses are retained and used to describe the topographical organisation of the visual cortex.

A model to describe the cortical responses between visual areas is the connective field (CF, Haak et al. 2013). CF modelling, also known as the cortico-cortical population receptive field, enables modelers to describe the response of a population of neurons in the cortex in terms of the activity in another region of the cortex. It translates the

concept of receptive field into the domain of connectivity by assessing the spatial dependency between signals in distinct cortical visual field regions. By using a similar approach to pRF, a circular symmetric 2D Gaussian on the cortical surface is used to define the CF parameters, position (v_0) and size (σ). The optimal CF parameters are estimated based on a procedure that fits the time series for each location in the target region (e.g. V2 or V3) using a linear combination of the time series in the source region (e.g. V1). Distances between locations in a source region are calculated across the cortical surface by using Dijkstra's algorithm (Dijkstra 1959). The CF parameters associated with the best fitting model are converted from cortical units (cortical position) into visual field units (eccentricity and polar angle). This is done by inferring the pRF properties of a centre voxel in the source region for each target location. The model pipeline and description are shown in Figure 3.

The translation of this technique into a Bayes framework is the main topic of **Chapters 2 and 3**. Both pRF and CF models are particularly important in the context of visual cortical plasticity in health and disease (Ahmadi et al. 2019; de Best et al. 2020; Halbertsma, Haak, and Cornelissen 2019). The application to a POAG population is reported in **Chapter 4**.

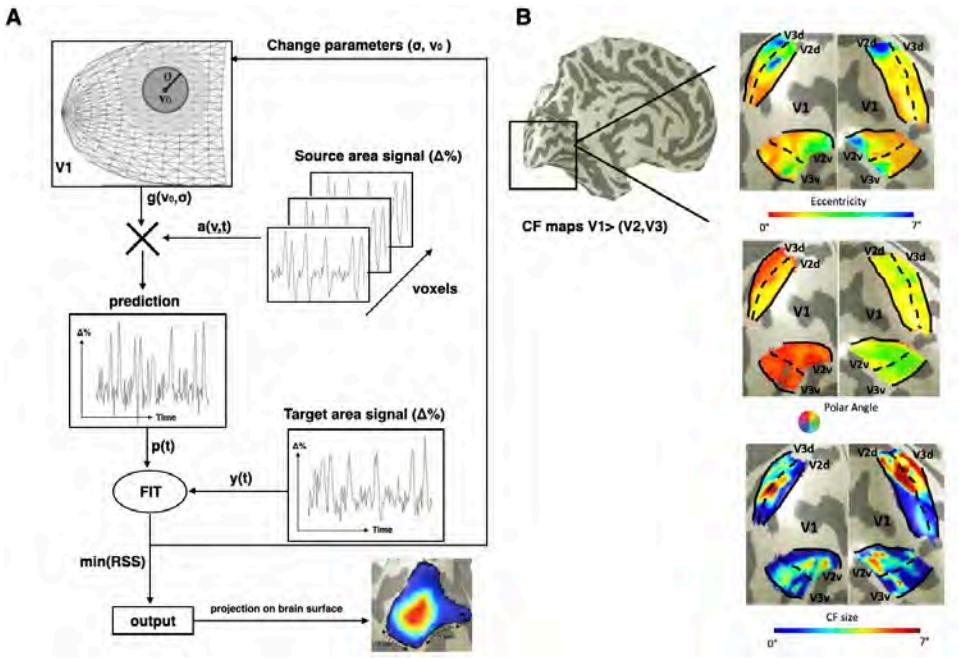

Figure 3 - CF model framework based on (Haak et al. 2013). Panel A: to estimate the CF, a linear spatiotemporal model and a 2D symmetric Gaussian CF model are used to create a predictive time series $p(t)$ which is fitted to the time series $y(t)$ of the target location. The predicted fMRI signal $p(t)$ is obtained by the overlap between the CF model $g(v)$ and the neural population inputs $a(v,t)$, that are defined as the BOLD time series per voxels (v). In particular, $g(v)$ is defined based on the shortest three-dimensional distance $D(v, v_o)$ between a voxel (v) and the proposed CF center (v_o)on a triangular mesh representation and σ, which defines the width of CF. By selecting the best fit between the predicted time series $p(t)$and the measured BOLD signal for each voxel of the target area, the optimal CF parameters are estimated. Panel B shows eccentricity, polar angle and CF size based on stimulus-driven data. These CF maps were obtained using V1 as source region while V2 and V3 served as target region.

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