Statistical approaches
for resting state fMRI data analysis

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"All models are wrong but some are useful."

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This doctoral dissertation investigates the methodology to explore brain dynamics from resting state fMRI data. A standard resting state fMRI study gives rise to massive amounts of noisy data with a complicated spatio-temporal correlation structure. There are two main objectives in the analysis of these noisy data: establishing the link between neural activity and the measured signal, and determining distributed brain networks that correspond to brain function. These measures can then be used as indicators of psychological, cognitive or pathological states. Each of these objectives is being approached through the application of various developed statistical methods: general linear model (GLM), functional and effective connectivity. GLM is a simple and powerful approach toward modeling the fMRI data, but its application relies on the exact timing of activity onset and duration, which is difficult to be obtained from resting state fMRI data without simultaneous electrophysiological recordings. Functional connectivity refers to the statistical dependence among the activity of different neural assemblies. Effective connectivity (EC) is a relatively new concept defined as the direct or indirect influence that one neural system exerts over another. It describes the dynamic directional interactions among brain regions. Concerning EC, several models have been proposed and validated: the direct transfer function, partial directed coherence, transfer entropy, Granger causality analysis, and dynamic causal models. All those methods can provide complementary insight on brains structure and function; most of them assume that the shape of the hemodynamic response function (HRF) is constant across all voxels and subjects. This may give rise to significant modeling errors in large parts of the brain, as the shape of the HRF may vary across both space and subjects. Apart from HRF confounding, redundancy is another issue that could mislead the connectivity estimation. When dealing with resting state fMRI datasets, we are always faced with high dimensionality and small sample size. A bivariate analysis would lead to the detection of many false positives, while a fully multivariate analysis could lead to computational problems due to the overfitting and the conceptual issues in presence of redundant variables.

We address HRF variability and redundancy in connectivity by using point process theory...
and information theory. The statistical characteristics of point processes for individual fMRI voxels are analyzed, then the corresponding spontaneous neural event onsets are derived. Finally, the variable HRF is retrieved using a GLM. A statistical analysis of HRF shape is further addressed, validated and applied to specific datasets. Finally, a HRF deconvolution is performed on the fMRI BOLD signal to recover the intrinsic neural signal, and then the connectivity network is constructed and analyzed on the deconvolved BOLD signal. The resulting connectivity network is thoroughly validated using ad hoc datasets.

Below, we give a brief outline of the thesis. The hemodynamic response function and brain connectivity are briefly reviewed in Chapter 1. The variability of HRF and redundancy in brain connectivity modelling are proposed for resting state fMRI data. The fundamentals of the resting state BOLD HRF are validated in Chapter 2 by considering simulated data, ASL data, simultaneous EEG-fMRI recordings, and eyes open and closed dataset. In Chapter 3, we present the modifications to the shape of the HRF at rest following modulations of consciousness. A combined study of hemodynamic response and Granger causality based effective connectivity on chronic back pain is contained in Chapter 4. A formal expansion of the transfer entropy to address the redundancy naturally inherent to fMRI data is presented in Chapter 5. Then a toolbox implementing both dynamic functional and effective connectivity for tracking brain dynamics from functional MRI (DynamicBC) is described in Chapter 6. Finally we summarize the findings across chapters and discuss implications and ideas for future research in Chapter 7.
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CHAPTER 1

General Introduction

1.1 Thesis objective

Neuroimaging is becoming a data-intensive science as its emphasis on collecting larger datasets and multimodal integration (Craddock et al., 2015). Thousands of brain imaging scans have been publicly shared so far. This enables us to investigate the neuroscientific questions that were previously inaccessible. Meanwhile, this growth is also quickly overwhelming the capacity of existing algorithms and tools to extract meaningful information from the data. Functional Magnetic Resonance Imaging (fMRI) is one of the most accumulated functional neuroimaging data. The high-dimensional fMRI data is typically characterized by a small sample size and high noise. It is an indirect and noisy measurement of brain activity, which captures the average effect of many spikes and does not resolve cortical columns, let alone individual neurons. A great statistical and computational effort is needed to infer the ground truth of neural activity from fMRI data (Lindquist, 2008). Nonetheless, fMRI has opened the door to quantitative yet non-invasive experiments on brain function (Ogawa et al., 1990). For instance, task-related fMRI enables us to identify and characterize functionally distinct areas in the human brain; resting state or task-free fMRI on the other hand shows lower signal noise ratio than task based fMRI, but has several advantages, especially for populations that can not perform behavioral or cognitive task (animals, development and clinical conditions). Additionally resting state fMRI is increasingly being recognized as a valid marker for clinical conditions and proxy for neural activations (Fox and Greicius, 2010; Lee et al., 2013b)). Most of resting-state fMRI studies focus on spontaneous low frequency fluctuations (≤0.1 Hz) in the blood oxygenation level dependent (BOLD) signal (Lee et al., 2013b). One of the most investigated topics is the functional architecture and of the brain derived from synchronous
activity between regions that are spatially distinct (van den Heuvel et al., 2008). However, there is evidence showing that high resting state BOLD synchronization is more likely to reflect tighter neurovascular connections (Tak et al., 2015), confirming the finding that the BOLD fluctuations depends on the contribution of neurovascular factors (Liu, 2013) (Figure 1.1). Hemodynamic response (HDR) is tightly linked with neurovascular coupling, as it reflects the complex interaction among cerebral blood flow, cerebral blood volume, and the venous oxygenation levels (Buxton et al., 1998). Even so, few studies consider the variance of hemodynamic response that may contribute to the correlations among these BOLD fluctuations. Without an explicit task design, retrieving hemodynamic response function (HRF) from resting state is a great challenge. One goal of this dissertation is to develop a set of state-of-the-art algorithms to retrieve HRF from resting state fMRI data. Another goal of this thesis concerns the improvement of the dynamical connectivity estimates at a fine scale in resting state fMRI data. As these data are typically characterized by high dimensionality and small sample size, bivariate analysis is the most employed approach to reconstruct functional architecture of the brain under stationary assumption. A large body research has shown that the nature of functional architecture is nonstationary (Hansen et al., 2015; Hutchison et al., 2013), and the bivariate method may mislead the inference of the information transfer when the effect of synergy and redundancy arise (Marinazzo et al., 2010, 2012; Stramaglia et al., 2014). To address these issue within the information theoretic framework, we aim to develop a simple and easily adoptable tools for analyzing dynamic brain networks. The ultimate goal is to obtain the maximum of information out of resting state fMRI data. In the rest of this chapter we will general overview the BOLD-fMRI, HRF model and brain connectivity.

1.2 Functional neuroimaging

Functional neuroimaging and related neuroimaging techniques are becoming important tools for brain research. Functional neuroimaging can be used to detect or measure cognition or behavior related changes in metabolism, blood flow, etc. The aim is to understand how the brain works under different condition (pathological, cognitive, behavioral, aging). These techniques include: electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET, include fludeoxyglucose for glucose metabolism, O-15 as a flow tracer, etc.), fMRI (include BOLD, perfusion, arterial spin labeling MRI, blood volume), optical imaging (near infrared spectroscopy, NIRS), functional photoacoustic microscopy, magnetic particle imaging, and transcranial magnetic stimulation (TMS), etc (Figure 1.2).

EEG and MEG have a high temporal resolution (milliseconds, accurate at recording fast changes in neural activity) but a relatively weak spatial resolution. And their source imaging is a challenge.
General Introduction

**Figure 1.1:** Blood supply to the human cerebrum. As illustrated here, the surface pattern of blood supply to the human cerebrum is highly complex. The red vessels are tributaries of the middle cerebral artery, the green vessels are tributaries of the anterior cerebral artery, and the blue vessels are tributaries of the posterior cerebral artery. The veins are shown in black (figure from (Huettel et al., 2004)).

**Figure 1.2:** Schematic diagram of brain signal detection mechanisms. EEG measures the electrical potential differences on the scalp that are generated by cortical neural activity. Neurons transmitting neurological signals across their synapses act as dipole sources. MEG detects the magnetic fields associated with such neuronal activation by SQUID sensors. fMRI measures the hemodynamic responses, particularly magnetic dynamics of protons (H+) related to neural activity; its technique is principally based on the detection of local BOLD signal contrast during neuronal activation. Using multiple arrays of optodes, NIRS characterizes changes in the intensity of attenuated near-infrared (IR) light (owing to scattering or absorption), resulting from changes in concentration between oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb) during local neural activity. (figure from (Min et al., 2010))
In contrast, PET has very low temporal resolution (tens of seconds to minutes), but reasonable structural accuracy (typically falls somewhere between that of fMRI and MEG/EEG), it directly reflects the current activity (measures the distribution of glucose or oxygen uptake in the brain by evaluating the number and timing of impact of the attached radioactive isotopes) and is able to measure blood flow, oxygen use, glucose metabolism, etc. PET scans are advantageous in that a person does not have to remain as still as he or she would for the fMRI. Tiny movements can obscure and ruin fMRI data but small movements do not affect PET scans. PET scan is more controversial than the other scans because it is rather costly, and requires injection of a trace amount of radioactivity and exposure to ionizing radiation.

FMRI has low temporal (hundreds of milliseconds or seconds) but relatively high spatial resolution. FMRI has come to dominate brain-mapping research because it does not require people to undergo shots, surgery, or to ingest substances, or be exposed to radiation, etc. fMRI can also be combined and complemented with other scans such as EEG, NIRS and PET. These hybrid-imaging technologies improve both spatial and time resolution.

1.3 BOLD-fMRI

![Figure 1.3: Left: summary of BOLD signal generation. Under normal conditions, oxygenated hemoglobin is converted to deoxygenated hemoglobin at a constant rate within the capillary bed (A). But when neurons become active, there is an increase in the supply of oxygenated hemoglobin above that needed by the neurons (B). This results in a relative decrease in the amount of deoxygenated hemoglobin and a corresponding decrease in the signal loss due to T2* effects. Right (C): Changes in oxygenated and deoxygenated hemoglobin following neuronal stimulation (figure from (Huettel et al., 2004)).](image-url)
One of the primary forms of fMRI uses the BOLD contrast, discovered by Seiji Ogawa (Ogawa et al., 1990). Increases in neural activity will elicit an increase in oxygen and glucose consumption supplied by the vascular system, then cause variations in microvascular oxygenation, more precisely, the ratio between oxygenated hemoglobin (diamagnetic) and deoxyhemoglobin (dHb, paramagnetic) changed, which in turn cause magnetization changes that can be detected in an MRI scanner. This method necessarily examines the oxygenation changes in venous blood because arterial blood is essentially completely oxygenated blood (oxygenation in arteries is always 90-100%) (McIntyre et al., 2003) (Figure 1.3).

It’s worth mentioning that the BOLD signal changes caused by neuronal processes are associated with synaptic inputs at the site of activation, not with the output level of firing of the neuron receiving synaptic inputs (Logothetis et al., 2001). This means that BOLD signal reflects the synaptic activity driving neuronal assemblies, but cannot disclose the information content of the neuronal firing patterns produced by the neurons (Ogawa and Sung, 2007), and indicates the relationship between the BOLD signal and a neural excitation or inhibition is not straightforward. However, accumulated evidences suggest that synaptic activity related to excitatory (EPSP) and inhibitory (IPSP) potentials leads to observe a positive BOLD response (Logothetis, 2003; Lauritzen, 2005); but a decrease in local neural activity leads to a negative BOLD response (Shmuel et al., 2006; Pasley et al., 2007). It is also possible for the BOLD signal to change without local neural activity changes, such as due to the physiological variations in cerebral circulation (Ogawa and Sung, 2007).

The previous studies show that BOLD changes detected in fMRI experiments vary around $1 \sim 10\%$. While some activation-induced signal changes will be contaminated by large surface vessel signals (reach very large value of $10 \sim 20\%$) (Figure 1.1) (Ogawa and Sung, 2007). Apart from the local vascular structure and brain anatomy, several other factors could also directly influence the BOLD signal: instrumental factors such as the magnetic field strength; the size of the voxels, and the age of the subject etc. Task parameters can also exert an influence on the magnitude of the BOLD signal change.

### 1.3.1 Hemodynamic response

The change in the MRI signal from neuronal activity is typically referred to as the hemodynamic response. There are some typical characteristics in stimulus-evoked HDR: it increases about $1 \sim 2$ second after neuronal activity and peaks up to plateau at about $5 \sim 8$s. In some cases, an initial decrease of the BOLD is observed call the initial dip, after the end of the stimulus, a poststimulus undershoot can often been observed (Figure 1.4, Top).

Though BOLD response offers only an indirect measure of the neural activity, it provides an interesting insight to the underling neural activity. Modeling the shape of HDR thus
plays an important role in the quantification of neural activity.

Figure 1.4: Top: BOLD HRF to an event stimulus applied at time $t = 0$s (figure from (Francis and Panchuelo, 2014)). Bottom: Relative changes in cerebral blood flow and cerebral blood volume following neuronal activity (figure from (Huettel et al., 2004)). CBF: cerebral blood flow; CBV: cerebral blood volume.

HDR is being studied almost from the beginning of fMRI. As mentioned before, several artifacts can corrupt BOLD-fMRI data; thus, it’s a great challenge to accurately and robustly model the HDR. There are two different approaches in modeling the hemodynamic response function in the literature. The most common approach is purely heuristic, using known functions (e.g. Poisson and Gaussian distributions (Friston, 1994; Rajapakse et al., 1998), and gamma functions (Boynton et al., 1996)). The second approach is biophysically informed non-linear models, such as the Balloon model (Buxton et al., 1998), which
describe the dynamic changes in dHb content as a function of blood oxygenation and blood volume (Figure 1.4, bottom). A more detail description of HRF model will be reviewed in the follow-up section.

### 1.3.2 Hemodynamic model

Considering the BOLD response linearly dependent on the underlying neural activity is a reasonable first approximation over restricted ranges (Boynton et al., 1996). Mapping of stimulus or task-related BOLD Changes become possible with a general linear model (GLM). Then the BOLD response to arbitrary stimulus can be predicted from stimulus/task time course and the systems impulse response function (i.e. HRF, \( h(t) \)) (Penny et al., 2011):

\[
X(t) = u(t) \otimes h(t) = \int_0^T u(t - \tau)h(\tau)d\tau
\]  
(1.1)

Where \( X(t) \) represents the predicted BOLD response arising from neural activity; \( u(t) \) indicate the stimulus function (usually the stick function or boxcar function encoding the occurrence of an event or epoch, \( u(t) = \sum_{i=1}^{K} \alpha_i \delta(t - t_i) \)), where \( \delta(t) \) is the Dirac delta function; \( \tau \) indexes the peristimulus time (PST), over which the BOLD impulse response is expressed.

Although the exact mechanisms underlying the HRF are not yet completely known, the HRF appears similar across early sensory regions, such as V1 (Boynton et al., 1996), A1 (Josephs et al., 1997) and S1 (Zarahn et al., 1997), these consistency of its observed shape allowed for canonical HRF models to be derived.

Among these HRF models, double Gamma models are the most frequently employed HRF in fMRI studies,

\[
h(t) = A \left( \frac{t^{\alpha_1-1}\beta_1^{\alpha_1}e^{-\beta_1t}}{\Gamma(\alpha_1)} - c \frac{t^{\alpha_2-1}\beta_2^{\alpha_2}e^{-\beta_2t}}{\Gamma(\alpha_2)} \right)
\]  
(1.2)

Where \( A \) controls the amplitude, \( \alpha \) and \( \beta \) control the shape and scale, respectively, and \( c \) determines the ratio of the response to undershoot. \( \Gamma \) represents the gamma function, which acts as a normalizing parameter. \( \alpha, \beta \) and \( c \) are fixed in canonical double Gamma HRF, which could not fully account for HRF variability and may lead to mis-modeling of the signal in large portions of the brain. However, as six parameters are involved in this model, the computation are more expensive, and optimal model fits can always result in physiologically ambiguous or implausible results, though there exist many excellent algorithms, such as Levenberg-Marquardt algorithm (Moré, 1978).

To accommodate the HRF variability, a simplest way to achieve this with GLM is via an
expansion in terms of $m$ temporal basis functions, $h_i(t)$:

$$h(\tau) = \sum_{i=1}^{m} b_i h_i(\tau)$$

Then the GLM equation in 1.1 can be written:

$$X(t) = \sum_{i=1}^{K} \sum_{j=1}^{m} b_j h_j(t - t^i)$$

Where $b_j$ are the parameters to be estimated. Several temporal basis sets are employed in fMRI studies, here only the following basis sets are introduced:

1. Canonical HRF with its partial derivatives used in SPM package, which allow for small shifts in both the onset and width of the canonical HRF. The fixed values ($\alpha$, $\beta$ and $c$) in canonical two gamma functions HRF were derived from a principal component analysis (PCA) of the data reported in (Friston et al., 1998b). For example, if the real BOLD impulse response is shifted by a small amount in time $\tau$, then by the first-order Taylor expansion: $h(t + \tau) \approx h(t) + \tau h'(t)$. Then small changes in the latency of the response can be captured by the parameter estimate for the temporal derivative. A similar logic applies to the use of dispersion derivative to capture (small) differences in the duration of the peak response. Together, these three functions comprise SPMs informed basis. Subsequent work, using more biophysically informed models of the hemodynamic response, revealed that the informed set is almost identical to the principal components of variation, with respect to the parameters of the Balloon model described in follow-up section (Penny et al., 2011).

2. FLOBS (FMRIBs Linear Optimal Basis Set) (Woolrich et al., 2004), which allows the specification of sensible ranges for various HRF-controlling parameters (delays and heights for the different parts of the HRF convolution kernel), generates lots of example HRFSs where each timing/height parameter is randomly sampled from the range specified, and then uses PCA to generate a basis set that optimally spans the space of the generated samples.

3. With the least assumptions about the shape of response: finite impulse response (FIR) and Fouries basis sets. However, optimal designs for estimation of their parameters are much more need than canonical HRF and FLOBS (Josephs and Henson, 1999; Miezin et al., 2000; Liu, 2004; Liu and Frank, 2004). In FIR model, the BOLD response of a certain voxel at time $t$ is the weighted sum of the stimulus values $(s_i, i \in [t - n + 1, t])$ at the preceding $n$ time points, i.e. $y_t(w) = \sum w_i s_{t-(i-1)} + w_0$. The optimal estimate of $w = [w_0, w_1, \cdots, w_n]^T$ is taken to minimize the total squared error between the observations and the model. To avoid overfitting problem in
the traditional least-square solution \( w = (S^T S)^{-1} S^T y \), Goutte et al. adopted a maximum a posteriori parameter estimation similar to ridge regression (Goutte et al., 2000), \( w_{MAP} = (S^T S + \sigma^2 \Sigma^{-1})^{-1} S^T y \), where \( \Sigma_{ij} = \upsilon \exp \left( -\frac{1}{2}(i - j)^2 \right) \), where \( h \) is a smoothing factor and Goutte recommends that this value be set a priori to \( h = \left( \frac{7 \tau_R}{2} \right)^{-\frac{1}{2}} \), \( \sigma^2 \) is the variance of noise, and \( \upsilon \) is the strength. Such a smoothing induces a correlation among parameters and prevents sudden changes in the local form of the HRF. So far, there are several convenient toolkits has been developed to perform the FIR related HRF recovery (Pedregosa et al., 2015; Vincent et al., 2014).

For a critical evaluation of these basis sets (especially the canonical HRF with partial derivatives, and FIR), see (Lindquist and Wager, 2007; Lindquist et al., 2009). These approaches could capture variations in HRF, but they do not provide a biophysical foundation for the HRF model, hence limiting the physiological interpretability of the associated parameters. Moreover, they do not explain empirically observed nonlinearities in the BOLD responses (Birn et al., 2001).

Nonlinearities are believed to arise from nonlinearities both in the vascular response and at the neuronal level (Sheth et al., 2004), and are commonly expressed as interactions among stimuli (Friston et al., 2000). In the presence of significant deviation from the expected linear system behavior, the GLM is not applicable for modelling BOLD signal. Using a biophysically informed model of the HRF can more accurately explains commonly observed non-linearities, and allows for a physiologically plausible interpretation of the results (Rosa et al., 2015). Then two main types of nonlinear models for fMRI have been proposed: the Ballon model and its extensions (Buxton et al., 1998, 2004), and the Volterra series based models (Friston et al., 2000).

The Balloon model is an input-state-output model; it describes the changes in blood oxygenation, cerebral blood flow and cerebral blood volume, as a consequence of the regional increase in brain metabolism associated with neuronal activity (Buxton et al., 1998). While the Volterra series model is an extension from the GLM, is a model for nonlinear behavior similar to the Taylor series. The second-order Volterra series are the most commonly used for simplicity, but flexible enough to accommodate a variety of nonlinear hemodynamic behaviors across different regions, stimuli and subjects (Friston et al., 2000; Zhang et al., 2014a). Unfortunately, due to much higher conceptual and computational complexity and higher number of state variables and parameters to be estimated (compare to GLM methods), these models have been usually remitted to studies in which the knowledge of the physiological events is important or essential.

In this dissertation, we only review the HRF model with linear and nonlinear framework. However, according to the different classified methods, the HRF model could be classified in different ways, such as parametric and nonparametric approaches (see (Zhang et al., 2014a).for a brief review).
1.3.3 Resting state HRF

The GLM-based method is dependent on the knowledge of stimulus function. For task related fMRI, the stimulus inputs (such as sensory stimuli or cognitive tasks) could be measured; while for resting state fMRI, no explicit external inputs exist. The simultaneous recordings of electrode may help to obtain resting state neural event information, also growing evidence indicates discrete neuronal events occur when the brain at rest (Deco and Jirsa, 2012; Tagliazucchi et al., 2012a; Petridou et al., 2013; Wu et al., 2013a). The corresponding spontaneous BOLD event can be detected by point process without multimodal monitoring (Tagliazucchi et al., 2012a; Wu et al., 2013a).

The dynamic Balloon model is a state-space model. Generalized filtering (Friston et al., 2010) and cubature Kalman filtering (Havlicek et al., 2011) has been proposed for the Balloon model inversion. Moreover, the information of stimulus inputs is not required in these methods. So it is another choice for resting state HRF analysis.

1.4 Brain mapping: from activation to networks

The GLM approach is one of the most common statistical methods to localize areas of the brain that activate in response to certain task. Apart from identification of the functional network of sites participating in a functional task, it can be also used to assess functional specificity of the activated sites by the carefully chosen paradigms (such as, to estimate whether the site only responds to a single psychological event type, or several types of events).

To understand how the brain works we also need to know the functional network of sites participating in a functional task, i.e. functional integration, or brain connectivity. A number of connectivity methods have been proposed to quantify information transfer among these sites. In the neuroimaging literature, the brain connectivity has been mainly characterized by anatomical, functional and effective connectivity. Anatomical connectivity is commonly based on white matter tracts quantified by diffusion tractography (Hagmann et al., 2008); functional connectivity relies on the other hand on statistical dependencies such as temporal correlation (Salvador et al., 2005). An important addition to this framework can come from effective connectivity analysis (Friston, 2011), in which the flow of information between even remote brain regions is inferred by the parameters of a predictive dynamical model.
1.4.1 Effective connectivity mapping

Granger causality

For some techniques, such as dynamic causal modelling (DCM) and structural equation modelling (McLntosh and Gonzalez-Lima, 1994; Buchel and Friston, 1997; Friston et al., 2003), these models are built and validated from specific anatomical and physiological hypotheses. Other techniques such as Granger causality analysis (GCA) (Bressler and Seth, 2011), are on the other hand data-driven and rely purely on statistical prediction and temporal precedence (Figure 1.5). While powerful and widely applicable, this last approach could suffer from two main limitations when applied to BOLD- fMRI data: confounding effect of HRF and conditioning to a large number of variables in presence of short time series.

Figure 1.5: Two fMRI signals with temporal dependence.

Early interpretation of fMRI based directed connectivity by GCA always assumed homogeneous hemodynamic processes over the brain; several studies have pointed out that this is indeed not the case and that we are faced with variable HRF latency across physiological processes and distinct brain regions (Roebroeck et al., 2011; Valdes-Sosa et al., 2011). Recently, a number of studies have addressed this issue proposing to model the HRF according to several recipes (Havlicek et al., 2010, 2011; Ryali et al., 2011; Kadkhodaian Bakhtiari and Hossein-Zadeh, 2012). As well, a recent study has proposed that it would still feasible to infer connectivity at BOLD level, under the assumption that Granger causality is theoretically invariant under filtering (Bressler and Seth, 2011) and that the HRF can be considered as a filter. It is still unclear whether and how specific effects related to HRF disturb the inference of temporal precedence. In addition a simulated or experimental ground truth is difficult to obtain, though some studies on simulated fMRI data have tried to reveal the relationship between neural-level and BOLD-level causal influence (Deshpande et al., 2010; Deshpande and Hu, 2012; Smith et al., 2011;
Wen et al., 2013). A considerable help to obtain the HRF for deconvolution could come from multimodal imaging where the high temporal resolution of EEG is combined to the high spatial resolution of fMRI, but this experimental approach is still far from being optimal and widely applicable. HRF has been studied almost since the early days of fMRI (Handwerker et al., 2012a). For task-related fMRI, neural population dynamics can be captured by modeling signal dynamics with explicit exogenous inputs (Riera et al., 2004; Friston et al., 2008) i.e. deconvolution according to the explicit task design is possible in this case (Glover, 1999; Friston et al., 2000). For resting-state fMRI on the other hand, the absence of explicit inputs makes this task more difficult, unless relying on some specific prior physiological hypothesis (Friston et al., 2008; Havlicek et al., 2011). To overcome this limitation, a novel blind deconvolution technique was developed recently for resting-state BOLD-fMRI signal (Wu et al., 2013a).

Coming to the second limitation, in order to distinguish among direct and mediated influences in multivariate datasets it is necessary to condition the analysis to other variables. A bivariate analysis would indeed lead to the detection of many false positives. In presence of a large number of variable and short time series, a fully multivariate conditioning could lead to computational problems due to the overfitting. Furthermore, conceptual issues would arise in presence of redundant variables (Angelini et al., 2010; Marinazzo et al., 2010; Stramaglia et al., 2014). To cope with redundancy and dimensionality curse in evaluating multivariate GC, it has recently been proposed (Marinazzo et al., 2012) that conditioning on a small number of variables, chosen as the most informative ones for each given candidate driver, can be enough to recover a network eliminating spurious influences, in particular when the connectivity pattern is sparse.

Transfer entropy

Transfer entropy (TE) is a rigorous derivation of a Wiener-Granger causal measure within the information theoretic framework (Schreiber, 2000). More specifically, transfer entropy from a process X to another process Y is the amount of uncertainty reduced in future values of Y by knowing the past values of X given past values of Y, i.e.

\[
TE_{X \rightarrow Y} = H(Y_t \mid Y_{t-1:t-L}) - H(Y_t \mid Y_{t-1:t-L}, X_{t-1:t-L})
\]

(1.5)

Where \( H(X) \) is Shannon entropy of X.

In principle, TE does not assume any particular model for the interaction between the two variable. Thus, the sensitivity of TE to all order correlations becomes an advantage for exploratory analyses over GC or other model based approaches. This is particularly relevant when the detection of some unknown non-linear interactions is required (Vicente et al., 2011). However, it usually requires more samples for accurate estimation (Pereda et al., 2005), which is one of the major obstacles to its application in fMRI data.
1.4.2 Dynamic brain connectome

Though it is often stated that dynamic interactions between brain regions constitute the basis of cognition, the majority of extant functional connections MRI studies assume temporal stationarity of connectivity metrics across a given period. A large body research has shown changes in connectivity metrics over time (Hutchison et al., 2013; Calhoun et al., 2014). Thus, the assumption that FC measures are constant over time is overly simplistic, and do not provide information critical to understanding how the brain produces cognition. What is needed is not only what is connected, but how and in what directions regions of the brain are connected: what signals they convey and how those signals are acted upon as part of a neural computational process (Bargmann and Marder, 2013; Kopell et al., 2014). Simulation and empirical studies indicate that functional connectivity dynamics bear promise to serve as a better biomarker of resting state neural activity and of its pathologic alterations (Hutchison et al., 2013; Zalesky et al., 2014; Hansen et al., 2015). These evidences suggest that dynamic FC metrics may index changes in macroscopic neural activity patterns underlying critical aspects of cognition and behavior, though limitations with regard to analysis and interpretation remain (Hutchison et al., 2013).
Retrieving the Hemodynamic Response Function in resting state fMRI: methodology and applications

Abstract

In this chapter we present a procedure to retrieve the hemodynamic response function from resting state (RS) fMRI data. The fundamentals of the procedure are further validated by a simulation and with ASL data. We then present the modifications to the shape of the HRF at rest when opening and closing the eyes using a simultaneous EEG-fMRI dataset. Finally, the HRF variability is further validated on a test-retest dataset.

2.1 Introduction

Functional MRI time series can be modeled as the convolution of a latent neural signal (which is not measured) and the hemodynamic response function (HRF). First, since the temporal characteristics of the HRF across different anatomical regions can be influenced by the underlying venous structure, it is possible that intrinsic activity across disparate brain regions can be temporally correlated owing to the underlying vascular architecture. Second, the hemodynamic response is affected by physiological fluctuations arising from cardiac pulsation and respiration (Cordes et al., 2001). These can introduce temporal correlations in fMRI signals. Also, given the fact that fMRI data is sampled slowly (typically every 1 ~ 2 seconds), physiological fluctuations cannot be removed by simple filtering as they can alias into the low frequency band of interest (0.01 ~ 0.1 Hz). Third, the period of the fastest variation in RS-fMRI data is 10 s, which is orders of magnitude greater than the sub-second time scale at which most neuronal processes occur. This
confounding effect can be dealt with by deconvolution of the HRF. In task-related fMRI this procedure has been known and applied since the very beginnings (Gitelman et al., 2003), since the onset of the HRF was known. This is not the case for RS-fMRI. Motivated by this evidence, we developed an approach to perform blind hemodynamic deconvolution of RS-fMRI data to recover the underlying latent neuronal signals (Wu et al., 2013a). This greatly improved the estimation of directed dynamical influences in RS-fMRI recordings, but also provided us with an estimation of the HRF shape for each voxel in the brain (Wu et al., 2013a). In this chapter we will first validate the blind HRF retrieval approach by means of a simulation and a comparison with baseline CBF, then we will analyze the effects of physiological conditions (eyes open vs. eyes closed) on the HRF shape; finally the HRF variability will be assessed with the help of a test-retest resting state fMRI dataset.

### 2.2 Methodology

The deconvolution is blind because there is no external input in case of RS-fMRI data and consequently, both the HRF and the underlying neuronal latent variables must be simultaneously estimated from the observed fMRI data, making this an ill-posed estimation problem.

We will now briefly review the foundations of a blind HRF retrieval technique for resting-state BOLD-fMRI signal developed in a previous work (Wu et al., 2013a). There is accumulated evidence of specific BOLD events governing the dynamics of the brain at rest (Tagliazucchi et al., 2012a; Petridou et al., 2013). We start from the assumption that resting-state brain dynamics can be driven by spontaneous events, which can be seen as a point process. A linear time invariant (LTI) system is used to model the relationship between the spontaneous neural event and the BOLD response. The hemodynamic response $h(t)$ represents such dynamic process; the BOLD signal at time $t$, $y(t)$, is modeled as the convolution of neural state $s(t)$ and $h(t)$, i.e.

$$y(t) = s(t) \otimes h(t) + \epsilon(t)$$  \hspace{1cm} (2.1)

where $\otimes$ denotes convolution, and $\epsilon(t)$ is the unexplained error.

The right side of the above equation includes three unobserved quantities. In order to solve the equation for $h(t)$ we need to substitute $s(t)$ with a hypothetical model of the neural activation for $s(t)$. Here we employ a stimulus function $\hat{s}(t)$ to model $s(t)$. $\hat{s}(t)$ is constituted by several time-shifted delta functions, which are centered at the onset of each spontaneous point process events. For task-related fMRI, the stimulus function is always derived according to the prior task design information. This is not the case for resting state fMRI. We need to retrieve the spontaneous point process event from a given signature (spike/peak) in the BOLD time series. As the peak of the BOLD signal lags
behind the peak of neural activation (i.e. \( \kappa \) seconds), it is reasonable to assume that these BOLD spikes are generated from the spontaneous point process events.

In order to obtain the time lag \( \kappa \), we search all values in the interval \([0, PST]\), where PST is the peristimulus time, choosing the one for which the noise squared error (i.e. \(| y(t) - \hat{s}(t) \otimes h(t) |^2 \)) is smallest, indicating the spontaneous event onset. In practice, The timing set \( S \) of these resting-state BOLD spikes/transients is defined as the time points exceeding a given threshold \( \mu \) around a local peak, which can be detected according to the following expression:

\[
S\{i\} = t^i, \ y(t^i) \geq \mu \ \& \ y(t^i) \geq y(t^i - \tau) \ \& \ y(t^i) \geq y(t^i + \tau)
\] (2.2)

It is worth mentioning that we make no assumption about the exact shape or functional form of the hemodynamic responses. The application of prior knowledge about possible hemodynamic response shapes could reduce the bias in the linear estimation framework especially for the low signal noise ratio dataset, and sharply reduce the computational cost.

Therefore, we assume that the hemodynamic responses for all resting state spontaneous point process events and at all locations in the brain are fully contained in an \( d \)-dimensional linear sub-space \( H \) of \( R^d \), then, any hemodynamic response \( h \) can be represented uniquely as the linear combination of the corresponding basis vectors. The canonical HRF with its delay and dispersion derivatives (we denote it as canon2dd) are employed as the basis functions in our previous study (Wu et al., 2013a). The HRF can also be reconstructed via (smoothed) Finite Impulse Response (sFIR) (Ciuciu et al., 2003; Lindquist and Wager, 2007) or 'selective averaging' (Dale and Buckner, 1997). There are some implicit limitations in our previous work described so far.

1. \( \epsilon \sim N(0, \sigma^2) \) is assumed to be white. However, \( \epsilon \) is not independent in time due to aliased biorhythms and intrinsic neural activity not accounted for in the model.

2. The spontaneous point process event onsets need to be synchronized with scans, i.e. the time lag \( \kappa \) is an integral multiple of TR, which may induce some bias.

3. in equation 2.1, the baseline activity is not included.

To reduce the above estimation bias, we modify the algorithm to account for the temporal dependency in \( \epsilon \), and the mismatching between events onset and scans, in the following way:

1. Using an \( AR(p) \) model during the parameter estimation of temporal correlation structure in \( \epsilon(t) \).

2. Estimating the time lag in a much finer temporal grid rather than TR, i.e. the peak of BOLD response lags behind the peak of neural activation is presumed to \( \kappa \times TR/N \) seconds (where \( 0 < \kappa < PST \times N/TR \)).
3. Adding a constant term into equation 2.1,

\[ y(t) = s(t) \otimes h(t) + c + \epsilon(t) \]  

(2.3)

where \( c \) indicates the baseline magnitude of the BOLD response.

To characterize the shape of the hemodynamic response, three parameters of the HRF, namely response height and its normalization (normalized by baseline magnitude \( c \), i.e. percent signal change, PSC), time to peak, Full Width at Half Maximum (FWHM), were estimated. These quantities are interpretable in terms of potential proxies for response magnitude, latency and duration of neuronal activity (Lindquist and Wager, 2007). The procedure described above is sketched in Figure 2.1.

![Figure 2.1: scheme of the resting state HRF retrieving procedure.](image)

### 2.3 Applications and Discussion

#### 2.3.1 Simulation

To validate the feasibility and effectiveness of proposed algorithm, the simulated HRFs are used as the ground truth for simulations. The HRF was generated using a physiological model, the balloon model (Buxton et al., 1998), with TR=2s and the parameters used SPM package: signal delay = 0.64, autoregulation= 0.32, exponent for \( F_{out}(v) = 0.32 \), resting oxygen extraction = 0.4, and varying transit time \( (\tau_0) = 0.98, 1.3, 1.6, 2 \). The transit time is \( V_0/F_0 \), where \( V_0 \) is resting blood volume fraction and \( F_0 \) is resting flow. The physiology of the relationship between flow and volume is determined by the evolution of the transit time (Friston et al., 2000). Two types of stimulus designs are employed to simulate the BOLD signal:
1. Event-related (ER) design (0.1s on) with fixed inter-stimulus-interval (ISI) of 40 s,
2. Jittered ER design with non-uniform ISI (average ISI = 19s).

Different levels of white noise $\epsilon$, modeled by an autoregressive AR(1) process with AR coefficient of 0.2, are added such that the resulting SNR ($\sigma_{\text{Signal}}/\sigma_{\text{Noise}}$, where $\sigma$ is the standard deviation) are 1.5 (low noise) and 0.1 (high noise). Each ER design simulation is run 20 times with random values of $\epsilon$ in order to generate a null distribution (in order to ensure reliability of the result and compute the mean and standard deviation of the HRF). We observed that the retrieved HRF shapes are dependent on the SNR. As expected, the variability of canon2dd HRF is much lower than sFIR model across all level of SNR, both for fixed and non-uniform ISI. As shown in Figure 2.2, two HRF basis vectors show similar but different degree of fitting of ground truth HRF, slightly vary with different transit times. These stable characteristics implicate that the proposed algorithm could be a robust indicator of spontaneous BOLD response. Besides, as the balloon model is a nonlinear HRF model, the jittered design may induce nonlinear interaction between stimuli, which could violate the assumption behind the proposed algorithm (Boynton et al., 2012).

### 2.3.2 Relation with cerebral blood flow

The BOLD-fMRI signal reflects the complex interactions between cerebral metabolic rate of oxygen, cerebral blood flow (CBF) and volume; the comparison of CBF and HRF in the same voxels could provide a better understanding of the temporal dynamics of resting state spontaneous responses. In this section we employ a public dataset (Avants et al., 2015) to explore the relationship between baseline CBF and HRF.

The resting state BOLD fMRI images were acquired using 2D EPI sequence (TR=2s, 8 min). Subjects (N=108, some of them with longitudinal data) were required to relax quietly while looking at a fixation point. Pseudo continuous arterial spin labeled (pCASL) images were acquired using gradient-EPI with TR/TE=4,000/12ms. The total imaging time was 5.5 min, and 40 label/control pairs were acquired, with 1.5s labeling duration and 1.2s post-labeling delay.

BOLD fMRI images were preprocessed with SPM12, including: realigning and unwarping, coregistration to anatomical image, spatial normalization into MNI space, smoothing (8 mm FWHM Gaussian kernel), detrending, and linear regression to remove possible spurious variances from the data (including six head motion parameters, non-neuronal sources of noise estimated using the anatomical component correction method, i.e. white matter and cerebral spinal fluid signal), 0.008 ~ 0.1Hz band filtering. As the slice order information is not reported in this dataset, we did not perform the slice timing correction, which does not affect the HRF retrieving algorithm anyway. pCASL data were preprocessed using the ASLtbx toolbox (Wang et al., 2008), with the following steps: realigning, coregistration to
anatomical image, regression of the six head motion parameters and smoothing with 6mm FWHM Gaussian kernel. CBF was then estimated, and finally normalization to MNI space was performed (same normalization method used in BOLD fMRI images). The group median map of CBF and HRF parameters are presented in Figure 2.3. We can observe that the HRF response height shows a spatial pattern similar to the CBF map. A prior functional parcellation of cerebrum is applied to the median map to validate the effect of spatial correlations between them. The prior functional parcellation is composed of seven large-scale subnetworks: visual (VN), somatomotor (SMN), dorsal attention (DAN), ventral attention (VAN), limbic (LN), frontoparietal (FPN) and default network (DMN) (Yeo et al., 2011). The correlation analysis across voxels in each subnetwork showed a striking spatial overlap between CBF and HRF response height (PSC, baseline) (Figure 2.4). Such phenomenon is not observed in other HRF parameters. In particular there is evidence of a highly nonlinear relationship between height PSC/baseline and CBF. In the DMN (baseline) and LN (height PSC), the linear relation is not evident, both for canon2dd and sFIR model. Furthermore, the across subject correlation between CBF and HRF were also analyzed both at voxel level and large-scale network level (Figure 2.5, 2.6). We found that different HRF models show different correlation with CBF at both spatial resolutions. In contrast to canon2dd, sFIR shows higher correlation in HRF response height, lower in time to peak. The physiological basis of this complicated interaction will need to be investigated further.

2.3.3 Relation with EEG power

In order to further investigate the electrophysiological basis of the HRF and its coupling to electrical brain activity we considered simultaneously recorded EEG and fMRI data. EEG were collected at 1000 Hz and down-sampled at 250 Hz. Scanner artifact correction, pulse artifact correction, notch filtering and ICA analysis were performed on the raw data. fMRI data were collected at 7 Tesla, with a repetition time of 1s. Resting-state fMRI data preprocessing was carried out using both AFNI and SPM8 package. First, the EPI volumes were corrected for the temporal difference in acquisition among different slices, and then the images were realigned to the first volume for head-motion correction. The resulting volumes were then despiked using AFNI’s 3dDespike algorithm to mitigate the impact of outliers. Next, the despiked images were spatially normalized to the Montreal Neurological Institute template then resampled to 3-mm isotropic voxels.

Several parameters were included in a linear regression to remove possible spurious variances from the data. These were i) six head motion parameters obtained in the realigning step, ii) non-neuronal sources of noise estimated using the anatomical component correction method (aCompCor, the representative signals of no interest from white matter (WM) and cerebral spinal fluid (CSF) included the top five principal components (PCs) from WM and
the top five from CSF mask; the subject-specific WM and CSF masks was segmented from the anatomical image of each participant using SPM8’s unified segmentation/normalization procedure) (Behzadi et al., 2007). Then the time series were temporally band-pass filtered (0.008∼0.1 Hz) and linearly detrended.

The scalp EEG voltage data from the three occipital channels O1, O2, and Oz were selected (Mo et al., 2013).

First, EEG signals for each channel were segmented into 500 ms non-overlapping epochs. Second, the EEG power spectrum for each single epoch was calculated using a nonparametric multitaper approach, and the alpha band power was obtained by integrating the power spectrum between 8 and 12 Hz. Third, the channel-level alpha power time series from each of the three occipital channels was averaged to yield the subject-level alpha power time series, which was convolved with a canonical hemodynamic response function (HRF). The HRF-convolved alpha power time series was then downsampled to the same sampling frequency as the BOLD signal. To identify brain regions whose BOLD activity co-varied with EEG alpha power, we examined the temporal correlation between HRF-convolved alpha power time series and BOLD time series from all voxels based on the general linear model (GLM). HRF-convolved alpha power time series was incorporated as a parametric regressor in the GLM, modeling the coupling effects between alpha and BOLD. The processed BOLD signal at every voxel was converted into its z-score, and the resting state HRF was retrieved as described above, according to the can2dd and sFIR model.

Two canonical ROIs were chosen from the previous GLM analysis (Thalamus and Occipital Lobe) (Laufs et al., 2003), both for eye closed and open conditions, under individual voxel p-value<10\(^{-6}\), cluster size>50. A positive correlation between BOLD and canonical HRF convolved alpha power was observed in the thalamus, and a negative one in the Occipital Lobe (Figure 2.7). After (can2dd and sFIR) HRF deconvolution, the Pearson correlation between devonvolved BOLD and alpha power is almost strengthened, only one weaken connectivity is found in thalamus with eye closed after can2dd HRF deconvolution (Figure 2.8). The voxel-level HRF shapes derived in these two regions in the two conditions are reported in Figure 2.9. We observed opposite patterns of HRF shapes between the thalamus and occipital cortex under the two conditions, which is consistent with the correlation and anti-correlation between the alpha power spectrum and BOLD signal in thalamic and occipital cortex. It is worth noting how the variations in HRF are consistent with the differences in net arterial and venous flow, and the consequent effects on the estimation of Granger causality reported in (Webb et al., 2013). This evidence confirms the importance of performing HRF deconvolution prior to estimating not only for lag-based directed connectivity (Wu et al., 2013a), but also for standard functional connectivity.
2.3.4 HRF modulations with eyes open and closed

In order to study the modulations of HRF shape when opening or closing the eyes on a larger sample, we considered a dataset of 48 healthy controls collected at the Beijing Normal University in China with 3 resting state fMRI scans of six minutes each (http://fcon_1000.projects.nitrc.org/indi/IndiPro.html). During the first scan participants were instructed to rest with their eyes closed. The second and third resting state scan were randomized between resting with eyes open versus eyes closed. Data were preprocessed as described in the above section. Then the resting state HRF was retrieved. Statistical significance of the spontaneous hemodynamic response evoked by opening and closing eyes was assessed with a group-level repeated-measures analysis of covariance (ANCOVA) that included subjects as the random factor and two fixed factors, resting state type (eyes closed and open) and order (eyes closed-open-closed, eyes closed-closed-open), age, gender, and mean framewise displacement (FD) power as the covariates. The ANCOVA revealed significant main effect for resting state conditions (eye closed/open) in hemodynamic response height. No significant main effect of order and interaction effect were found. The significant differences in the height of the HRF located in the occipital areas, which were depicted in figure 2.10. The corresponding HRF shape is also reported. Though the difference in the thalamus is not obvious, we still can find the opposite patterns of HRF shapes under eye closed and open, similar with the finding in EEG-fMRI dataset.

2.3.5 HRF variability

The hemodynamic response has been shown to vary in timing, amplitude, and shape across brain regions and cognitive task paradigms (Miezin et al., 2000; Handwerker et al., 2012a; Badillo et al., 2013). Such variation is expected also for resting state. In order to investigate the variability on the resting state HRF, test-retest (TRT) reliability analyses were performed on a resting-state fMRI dataset that has been publicly released in the '1000 Functional Connectomes Project'. All included participants had no history of neurological and psychiatric disorders and all gave the informed consent approved by local Institutional Review Board. During the scanning participants were instructed to keep their eyes closed, not to think of anything in particular, and to avoid falling asleep. Two data sets with different TR (TR = 2.5 s and TR = 0.645 s) were acquired on Siemens 3T Trio Tim scanners using standard EPI sequence (TR = 2500msec, 3mm isotropic voxels, 5 minutes) and multiband EPI sequence (TR = 0.645 s, 3 mm isotropic voxels, 10 min). To evaluate the test-retest reliability of the voxel HRF parameters between the two sessions, a measurement of the intraclass correlation coefficient (ICC) was employed. A one-way ANOVA with random subject effect was used to compute the between-subject mean square (BMS) and within-subject mean square (WMS). Then an ICC(3,1) value was subsequently
Retrieving the HRF in rs-fMRI calculated according to the equation (Shrout and Fleiss, 1979)

\[ ICC = \frac{BMS - WMS}{BMS + (m - 1)WMS} \]  \hspace{1cm} (2.4)

where \( m \) represents the number of repeated measurements of the voxel HRF parameter (here, \( m = 2 \)). We calculated the ICC value for each voxel and generated the ICC map for each HRF parameter. Next, the TRT reliability of the HRF parameter was assessed in a voxel-wise manner with the classifying criteria of ICC values (Sampat et al., 2006): less than 0.4 indicated low reliability; 0.4 to 0.6 indicated fair reliability; 0.6 to 0.75 indicated good reliability and 0.75 to 1.0 indicated excellent reliability. To further assess the regional variability of TRT reliability, we utilized the above-mentioned prior functional parcellation of cerebrum, and calculated the mean ICC values and their standard deviations within these subnetworks, respectively. As was expected, sFIR showed lower ICC than canon2dd model, both at voxel level and large-scale network level. We did not observe an obvious spatial pattern in the ICC maps for distinct networks (Figures 2.11-2.12). The hemodynamic response height (PSC) showed good reliability for canon2dd model across all subnetworks and TR (excluding the VN at TR=2.5s), and for sFIR in VAN, FPN and DMN at TR=2.5s, and fair reliability for most of the subnetworks with sFIR model (Figure 2.11). The other HRF parameters (FWHM and time to peak) showed low reliability. These results reveal that the different hemodynamic response sampling (i.e. in units of TR) only slightly affects the ICC maps of hemodynamic response height.

2.4 Conclusions and future work

We have presented a methodology to retrieve the hemodynamic response function from resting state fMRI data. The feasibility and effectiveness of proposed algorithm is confirmed by simulation data. The results are promising since the retrieved HRF is consistent with the literature and supports evidences of the vascular flow. Additionally, functional modifications to the HRF shape are consistent with evidence previously reported using different methodologies. The approach will need further validation using electrophysiological and cardiovascular data.
Figure 2.2: shows (a) ER stimulus timing, the ideal BOLD response, and ideal response corrupted with noise (SNR=1) (b) Ground truth (Balloon) and estimated HRFs for fixed ISI ER design, (c) Ground truth and estimated HRFs for jittered ER design. The colored shadow indicates the standard deviation.
Retrieving the HRF in rs-fMRI

(a)
Retrieving the HRF in rs-fMRI

Figure 2.3: Median maps of CBF and HRF parameters across subjects.
Figure 2.4: Scatterplot of the spatial correlations across voxels between CBF and HRF parameters. X-axis is the CBF, Y-axis are the HRF parameters. Blue scatterplot indicate the linear correlation is significant, $p < 0.05$ corrected.
Figure 2.5: Scatterplot of the across subject correlations between CBF and HRF parameters. X-axis is the CBF, Y-axis are the HRF parameters. Blue scatterplots indicate the linear correlation is significant, $p < 0.05$ corrected.
Figure 2.6: Correlations between CBF and HRF parameters at voxel level across subjects. The upper colorbar is for inside plots, the bottom colorbar is for surface plots.
Figure 2.7: clusters of significant correlation (red) and anti-correlation (blue) between BOLD and alpha power spectrum

Figure 2.8: Pearson correlation between (BOLD) Deconvolved BOLD signal and (canonical HRF convolved) alpha power. Occ: occipital area; Thal: thalamus; Cc: eyes closed, canon2dd; Cs: eyes closed, sFIR; Oc: eyes open, canon2dd; Os: eyes open, sFIR.
Figure 2.9: HRF at rest in the occipital cortex (left) and in the thalamus (right) for eyes open and closed. Left upper pannel is HRF estimated by sFIR model, the bottom pannel is HRF estimated by canonical HRF with its derivatives. The red and blue shadows are the standard deviations of voxelwise HRFs under eyes closed and open conditions.
Figure 2.10: Statistical differences in HRF height with eyes closed (1), open, then closed again (2) (top), and typical shapes in the occipital (left) and thalamic (right) area (middle: sFIR; bottom: canonical HRF with its derivatives).
Figure 2.11: TRT reliability of HRF parameters within seven subnetwork. C-TR645: canon2dd HRF, TR=0.645s; S-TR645: sFIR HRF, TR=0.645s; C-TR25: canon2dd HRF, TR=2.5s; S-TR25: sFIR HRF, TR=2.5s; T2P: Time to peak.
Figure 2.12: TRT reliability maps of hemodynamic response height (PSC) with different HRF basis vector \( s(\text{canon2dd}, \text{sFIR}) \), at different TR (0.645s, 2.5s).
CHAPTER 3

Modulated spontaneous hemodynamic response to loss of consciousness

Abstract

Functional imaging has already accumulated abundant research results on the neural correlates of consciousness. Apart from task-related activation derived in fMRI, PET based glucose metabolism rate or cerebral blood flow account for a considerable proportion in the study of brain activity under different level of consciousness. Resting state functional connectivity MRI is playing a crucial role to explore the consciousness related functional integration. So far, a comparatively comprehensive and systematic comparison of brain activity measured by PET and BOLD-fMRI in the resting state has never been done. Here, spontaneous hemodynamic response is introduced to characterize resting state brain activity, then used to investigate the loss of consciousness under propofol anesthesia and vegetative state. The previous PET results on anesthesia or pathology induced loss of consciousness are validated by resting state hemodynamic response. The dysfunction of hemodynamic response in precuneus and posterior cingulate is found to be a common principle underlying loss of consciousness in both conditions. The thalamus appears to be less obviously modulated by propofol, compared with frontoparietal regions. However, a significant reduction in spontaneous thalamic hemodynamic response was found in vegetative state.
3.1 Introduction

It is crucial to understand the physiologic basis of consciousness in pathological or pharmacological coma, which may provide effective assistance to diagnosis, prognostication, and assess potential treatments. The advanced neuroimaging techniques have significantly expanded our knowledge of neural correlates of conscious level in human brain. For instance, FDG-PET imaging and fMRI have shown that altered metabolism and connectivity in thalamus, frontoparietal and default mode network (Laureys, 2005; Laureys et al., 2000a,b, 2002, 2004) are found in patients with disorders of consciousness, electrophysiological techniques have discovered some covert rhythm signs of consciousness (Gugino et al., 2001; Vijayan et al., 2013). Finding high test-retest reliable evidences within or across multimode imaging are the necessary step to obtain the clinically applicable neural markers of consciousness. Such work has gained extensive attention and not confined to consciousness, especially in the fMRI studies (Plichta et al., 2012). A clinical validation study reveals that PET imaging show higher diagnostic precision than fMRI in disorders of consciousness (Stender et al., 2014). This indicates much more underlying dynamic information mining should be explored with advanced fMRI model, considering that spatiotemporal resolution is more excellent with fMRI than PET.

Consciousness has two major components: awareness of environment and of self (i.e. the content of consciousness) and wakefulness (i.e. the level of consciousness) (Laureys, 2005). The vegetative state is the most tragic model that dissociates wakefulness and awareness. The accumulated neuroimaging evidences revealing how them could be separated in vegetative state (VS), mainly deriving from the correlation between awareness and global brain function (Laureys et al., 1999a), regional brain function, brain activation induced by passive external stimulation (Laureys and Schiff, 2012) or mental imagery task (Owen et al., 2005), changes in resting state connectivity (Laureys et al., 2000b, 1999a,b). While the anesthetic drugs manipulation to achieve specific state of consciousness is another direct way to explore qualitative nature of consciousness (Alkire and Miller, 2005), similar brain imaging techniques as applied in VS are used to identify neural correlates of consciousness (Boveroux et al., 2010; Hudetz, 2012; DiFrancesco et al., 2013). Compare to global brain metabolism, regional metabolic dysfunction is a more reliable maker of individual conscious-unconscious state transition (Laureys, 2005). The studies of passive stimuli have shown promising results, especially for minimally conscious state patients, but the neuronal responses cannot be always stable (Laureys and Schiff, 2012) then the followed inference of cognitive function from these cerebral activations is controversial (Menon et al., 1999; Schiff and Plum, 1999). Resting state functional connectivity (FC) play a critical role in the quantification of brain function integration that maintaining the state of consciousness (Laureys et al., 2000b, 1999a,b; Boveroux et al., 2010), and well confirmed the previous FDG-PET results (Laureys and Schiff, 2012). Nevertheless, brain connectivity are now
facing more challenges, such as the neurovascular connection anatomy (Tak et al., 2014) and motion artifact (Power et al., 2012) may contribute high proportion to observed FC. BOLD-fMRI hemodynamic response describe the vascular oxygenation changes to a neuronal impulse response, is a more relevant measure of neural activity with PET. To validate and confirm the cerebral metabolic patterns of altered level of consciousness observed in PET studies from a different neuroimaging technique, we investigate the hemodynamic response pattern in VS patient and the healthy subjects with propofol anesthesia using resting state fMRI data. The hemodynamic response correlates of consciousness will be explored and compared between vegetative state and anesthesia. According to the previous PET studies (Boly et al., 2011; Laureys, 2005; Laureys et al., 2004), we hypothesis thalamus, fronto-parietal cortical areas and default mode network (DMN) will exhibit state-dependent spontaneous hemodynamic response in the resting state.

3.2 Materials and Methods

3.2.1 Subjects

Twenty-one healthy right-handed volunteers, twenty coma patients and thirty two healthy controls participated in the study. The subjects provided written informed consent to participate in the study. None of the healthy subjects had a history of head trauma or surgery, mental illness, drug addiction, asthma, motion sickness, or previous problems during anesthesia. The study was approved by the Ethics Committee of the Medical School of the University of Liege (University Hospital, Liege, Belgium).

3.2.2 Functional Data Acquisition

The propofol dataset considered in current study has already been published in (Boveroux et al., 2010). Functional MRI acquisition consisted of resting-state fMRI volumes repeated in four clinical states only for 21 healthy volunteers: normal wakefulness (W1), mild sedation (S1), deep sedation (S2), and recovery of consciousness (W2). The temporal order of mild- and deep-sedation conditions was randomized. The typical scan duration was half an hour in each condition. The number of scans per session was matched in each subject to obtain a similar number of scans in all four clinical states (mean ± SD, 251 ± 77 scans/session). There is only one session of resting state fMRI for each subject in VS dataset, each one contains 297 scans. All functional images were acquired on a 3 Tesla Siemens Allegra scanner (Siemens AG, Munich, Germany);

- Propofol dataset: Echo Planar Imaging sequence using 32 slices; repetition time (TR)=2460ms, echo time=40ms, field of view = 220mm, voxel size=3.45x3.45x3
mm, and matrix size=64×64×32).

- VS dataset: Echo Planar Imaging sequence using 32 slices; repetition time (TR)=2000ms, echo time=30ms, field of view = 384mm, voxel size=3.44×3.44×3 mm, and matrix size=64×64×32).

### 3.2.3 Data Preprocessing

All structural images in both datasets were manually reoriented to the anterior commissure and segmented into grey matter, white matter (WM), cerebrospinal fluid (CSF), skull, and soft tissue outside the brain, using the standard segmentation option in SPM 12. Then a DARTEL template was created based on the deformation fields that are produced during the segmentation procedure. Resting-state fMRI data preprocessing was subsequently carried out using both AFNI and SPM12b package. First, the EPI volumes were corrected for the temporal difference in acquisition among different slices, and then the images were realigned to the first volume for head-motion correction. 8 VS patients and 7 healthy control subjects were excluded from the dataset because either translation or rotation exceeded ±1.5 mm or ±1.5°, or mean framewise displacement (FD) exceeded 0.3, resulting in 12 VS patient and 25 healthy controls which were used in the analysis, and 22 sessions in propofol group subjects were also excluded. The resulting volumes were then despiked using AFNI’s 3dDespike algorithm to mitigate the impact of outliers. The mean BOLD image across all realigned volumes was coregistered with the structural image, and the resulting warps applied to all the despiked BOLD volumes. Finally all the coregistered BOLD images were smoothed (8 mm full-width half-maximum) and spatially normalized into MNI space. Several parameters were included in a linear regression to remove possible spurious variances from the data. These were i) six head motion parameters obtained in the realigning step, ii) non-neuronal sources of noise estimated using the anatomical component correction method (aCompCor, the representative signals of no interest from subject-specific white matter (WM) and cerebral spinal fluid (CSF) included the top five principal components (PCs) from WM and the top five from CSF mask) (Behzadi et al., 2007). Then the residual time series were linearly detrended and temporally band-pass filtered (0.008-0.1 Hz).

### 3.2.4 Spontaneous point process event and HRF retrieval

We employ a blind hemodynamic response function (HRF) retrieval technique specially developed for resting-state BOLD-fMRI signal (Wu et al., 2013a), which considers the resting-state BOLD signal as driven by spontaneous point process events. A linear time-invariant model for the observed resting state BOLD response is assumed (Boynton et al., 1996; Dale and Buckner, 1997). We consider a common HRF is shared across the various
spontaneous point process events at a given voxel, which could result in more robust estimation. The BOLD-fMRI signal $y(t)$ at a particular voxel is given by:

$$y(t) = s(t) \otimes h(t) + c + \epsilon(t)$$

(3.1)

where $x(t)$ is a sum of time-shifted delta functions, centered at the onset of each spontaneous point process event and $h(t)$ is the (unknown) hemodynamic response to these events, $c$ is constant term indicating the baseline magnitude of the BOLD response, $\epsilon$ represents additive noise and $\otimes$ denotes convolution. The noise errors are not independent in time due to aliased biorhythms and unmodelled neural activity, and are accounted for using an AR($p$) model during the parameter estimation (we set $p = 2$ in current study). In practice, $y(t)$ is not sampled continuously in time, but rather at discrete intervals, i.e. TR. Consequently, the convolution was performed in TR temporal resolution in our precious study (Wu et al., 2013a). Given that spontaneous point process event onsets do not need to be synchronized with scans, here we perform the convolution at a higher temporal resolution with $N$ time points per scan then down-sampled to TR temporal resolution at Equation 3.2. Although no explicit external inputs exist in resting-state fMRI acquisitions, we still could retrieve the timing of these spontaneous events by blind deconvolution technique (Wu et al., 2013a).

The peak of BOLD response lags behind the peak of neural activation is presumed to $\kappa \times TR/N$ seconds (where $0 < \kappa < PST \times N/TR$, peristimulus time, PST). The timing set $S$ of these resting-state BOLD transients is defined as the time points exceeding a given threshold around a local peak, can be detected by the following way: $S\{i\} = t^i$, $y(t^i) \geq \mu$ & $y(t^i) \geq y(t^i - \tau)$ & $y(t^i) \geq y(t^i + \tau)$, where we set $\tau = 1, 2$ and $\mu = \sigma$ (i.e. SD) in current study. While the exact time lags can be obtained by minimizing the mean squared error of equation 3.1, i.e. the optimization problem:

$$\hat{h}, \hat{\kappa} = \arg\min_{h, \kappa} | y(t) - \hat{s}(t) \otimes h(t) - c |^2$$

(3.2)

In order to escape motion artifacts induced pseudo point process events, a temporal mask with $FD < 0.3$ was added to exclude these bad pseudo-event onsets from timing set by means of data scrubbing (Power et al., 2012). A schematic diagram to retrieve the spontaneous point process events is shown in figure 3.1. The method described above makes no assumptions about the exact shape or functional form of the hemodynamic responses. The application of prior knowledge about possible hemodynamic response shapes could reduce the bias in the linear estimation framework especially for the low signal noise ratio dataset, and sharply reduce the computational cost. Here we assume that the hemodynamic response for all resting state spontaneous point process events and at all locations in the brain are fully contained in an $d$-dimensional linear sub-space $H$ of $\mathbb{R}^d$, then, any hemodynamic response $h$ can be represented uniquely as the linear combination of the corresponding basis vectors. The canonical HRF in SPM with its delay
and dispersion derivatives are employed as the basis functions in current study (Friston et al., 1998a) (we denote it as canon2dd model), the more flexibly smoothed FIR (sFIR) model is also included to minimize the risk of assumptions about the HRF shape (Goutte et al., 2000). To characterize the shape of hemodynamic response, three parameters of the HRF, namely response height (normalized by baseline magnitude, i.e. percent signal change), time to peak, Full Width at Half Maximum (FWHM), were estimated, and could be interpretable in terms of potential measures for response magnitude, latency and duration of neuronal activity (Lindquist and Wager, 2007).

Figure 3.1: Left panel: red horizontal dashed line is the threshold (mean+SD), red vertical dashed line represents the point process, Purple lines indicate the pseudo neural event onset time (before than the BOLD point process). each signal shown here come from a voxel in precuneus (MNI coordinate [-3 -54 33]), the first four row comes from the same subject. Due to motion artifact, some above-threshold time points are scrubbed. Right panel: group averaged HRF with its standard error (the HRF come from the same voxel shown in left pannel), the left is from propofol dataset, and the right is from VS dataset. The first row HRFs are estimated by canonical HRF with its derivative, the second row HRFs are modeled by smoothed FIR.

3.2.5 Statistical Analysis

We retrieved resting state HRF for all the voxels contained within the cerebrum using AAL template (Tzourio-Mazoyer et al., 2002). HRF parameters for each subject individually were entered into a random-effects analysis (one-way ANOVA within subjects, with three covariate (age, gender and mean FD) to identify regions which showed significant activity differences among four clinical states), a linear T contrast was computed, searching for a linear relationship between HRF and the level of consciousness across the four conditions (constrast (W1 W2 S1 S2): [1.5 0.5 1.5 -0.5]) (Boveroux et al., 2010). Meanwhile, pairwise t-test between W1 and S2 was further performed to compare with the results from VS
dataset. A two-sample t-test with three covariates (age, gender and mean FD (Power et al., 2012)) was implemented to map group difference of HRF parameters between control subjects and VS patients. The consistent group difference maps from different HRF models and datasets were obtained using conjunctions (minimum statistic compared to the conjunction null) (Nichols et al., 2005). Type I error due to multiple comparisons across voxels was controlled by false discovery rate method (Chumbley et al., 2010). Statistical significance for group analysis was set at $P_{FDR} < 0.05$, derived from the Gaussian random field theory.

### 3.3 Results

A two-sample Wilcoxon rank sum test revealed no statistically significant differences in age and gender between VS and control groups, under the null hypothesis at the 5% significance level).

#### 3.3.1 Spatial distributions of resting state HRF

The temporal interval of spontaneous point process events is present in an inhomogeneous distribution (Figure 3.2), which enabled a robust GLM estimation for HRF retrieving. HRFs are modeled using either canonical HRF basis, or sFIR model. HRF parameters of each voxel are estimated and mapped on the brain (Figure 3.3). The median maps of each HRF parameters exhibit spatially heterogeneity across different level of consciousness and HRF models (Figure 3.3). The similar distributions are presented in W1, W2 and control group, higher response height and FWHM are shown in frontal lobe and precuneus.

#### 3.3.2 Group HRF differences and Conjunction

Statistical maps of HRF parameters reveal that HRF shapes are modulated due to propofol anesthesia (Figure 3.4). The linear covariation between HRF and the level of consciousness only distributed on specific brain area, further conjunction analysis reveals such phenomenon only occurred in the response height. These correlated region are in frontal lobe (middle/medial/inferior/superior frontal gyrus), anterior cingulate, inferior parietal lobule, precuneus, posterior cingulate, supramarginal gyrus, angular gyrus; Due to finer temporal resolution, the linear relationship could also be found in FWHM with canon2dd model in the frontal gyrus (medial/middle/inferior/superior) and anterior cingulate (Figure 3.6.A). There is no linear relationship found from both two HRF model in temporal latency of hemodynamic response. The conjunction analysis indicates group pairwise differences between W1 and S2 present a similar map shown in the above linear covariation map (Figure 3.5).
3.2 The frequency distribution of temporal interval between these adjacent point process events. Only one subject used in the plot.

The VS subjects show lower spontaneous response height than control subjects in precuneus, inferior parietal lobule, and angular gyrus, but higher response height in putamen, thalamus, and anterior cingulate with the conjunction analysis of two HRF models. While the sub-regions of frontal gyrus exhibit contrary different patterns in spontaneous hemodynamic response height between VS and control group (Figure 3.7). In contrast to VS group, the control subjects show broader response width (FWHM) in precuneus, posterior cingulate, inferior parietal lobule, supramarginal gyrus, but only be found with canon2dd HRF model (Figure 3.6.B). There is no group difference found from both two HRF models in the time to peak of hemodynamic response. A conjunction analysis for W1 minus S2 and Control minus VS contrasts yielded significant cluster of higher spontaneous response height in precuneus and posterior cingulate (Figure 3.8).

3.4 Discussion

We investigated consciousness related resting state hemodynamic response based on the BOLD fMRI signals in healthy control with propofol anesthesia and patient under vegetative state. The hemodynamic response showed similarities and differences in pharmacological and pathological induced loss of consciousness. We found the dysfunction of hemodynamic response in precuneus and posterior cingulate is a common principle underlying loss of consciousness induced by propofol anesthesia and vegetative state, which is consistent
Modulated spontaneous hemodynamic response to loss of consciousness

Figure 3.3: Median map of HRF parameters (response height, FWHM, time to peak), estimated by canon2dd and sFIR model. Each dataset and HRF parameter use the different color limits, the same color limit is set up for the same HRF parameter and dataset. For better comparison, the maximum value in colormap is not the maximum value of HRF parameters.

with previous PET and functional connectivity MRI studies (Fiset et al., 2005; Laureys, 2005). The hemodynamic response in frontoparietal networks are obviously altered with propofol anesthesia, but changes in subcortical regions like the thalamus are not obvious. However, the spontaneous thalamic hemodynamic response exhibit distinctly different characteristic between healthy controls and VS patient. Critically, our results for the first time show that anesthesia or pathology induced neurovascular coupling could be tracked by modulated spontaneous hemodynamic response derived from resting state fMRI. These results demonstrate the feasibility of resting state HRF for the study of the brain at rest, revealing comprehensive and complementary information to further decode anesthetic or and pathological brain function. It is well established that most anesthetic agents decrease glucose metabolism in a dose-dependent manner with variable effect on glucose metabolism rate (GMR) and cerebral blood flow (CBF) (Alkire and Miller, 2005). While the BOLD-fMRI signal reflect the complex interactions between cerebral metabolic rate of oxygen, cerebral blood flow and volume (Ogawa et al., 1990). Therefore, the changes that occur in the brain metabolism and CBF caused by neural activity could be accompanied
by concurrent changes in BOLD effect in a predictable way. Most fMRI studies employ active or passive paradigm to detect activation in sensory or cognitive system (Laureys and Schiff, 2012). However the quantifiable natures of relation between cerebral metabolism and resting state BOLD-HRF has been left largely unexplored.

Many studies focused on regional GMR and CBF with PET to measure anesthesia or pathology induced unconsciousness (Alkire and Miller, 2005; Laureys, 2005). In the unconscious state, the consistent regions that show relative decreases of metabolism and blood flow are in the frontoparietal networks, defaults mode network, as well as the thalamus (Laureys et al., 2004; Alkire and Miller, 2005; Nakayama et al., 2006). These regions are involved in conscious processing. The loss of consciousness suggests a disturbance in the optimal balance between segregation and integration among these regions and the connected regions. Such as DMN is considered to be involved in stimulus-independent thought, mind-wandering and self-consciousness (Raichle, 2015). The posterior cingulate cortex (PCC) and the medial precuneus are prominent features of the DMN, they act as a core hub role in integrating information across functionally segregated brain regions, display high resting metabolically active. PCC has dense structural connectivity to widespread brain regions, is involved in internally directed thought (Leech et al., 2012), and engaged in continuous information gathering and representation of the self and external world with interconnected precuneus and medial prefrontal cortices (Gusnard et al., 2001).

**Figure 3.4**: Conjunction map (canon2dd and sFIR) of linear correlation between response height and four levels of consciousness (w1, w2, s1, s2), $p < 0.05$, topo FDR correction.
Figure 3.5: Conjunction map (canon2dd and sFIR) of response height differences between w1 and s2, $p < 0.05$, topo FDR correction.

Figure 3.6: (A) linear correlation between FWHM and four levels of consciousness (w1, w2, s1, s2), $p < 0.05$, topo FDR correction. (B) Group differences of FWHM between healthy controls and VS patients, $p < 0.05$, topo FDR correction. A and B are based on the canon2dd HRF model.

The precuneus is one of the first regions of the brain to resume activity when regaining consciousness from a vegetative state, and together with the adjacent PCC are the regions that differentiate patients in minimally conscious states from those in VS (Laureys et al., 2004). Therefore, the consistent founding in decreased hemodynamic response in precuneus and posterior cingulate indicates the deficits in cognitive functioning and information integration that lead to a total breakdown of consciousness.
The thalamus plays an important role in normal arousal regulation (Schiff, 2008), thus is always the common locus of action of brain injury in vegetative state and of general anesthetics. Its anatomy and physiology imply a central role in consciousness (Ward, 2011). Certainly the thalamic activity are identified as a key target of anesthetic effects on consciousness. However, thalamic depression may depend on the agent studied and the degree of sedation. It has been suggested that cortical cells are more sensitive to the effect of propofol than sub-cortical elements (Sun et al., 2008; Alkire and Miller, 2005). Our finding confirms such phenomenon, it shows that spontaneous hemodynamic response in frontal lobe is significant correlated with propofol anesthesia, but such effect cannot be identified in thalamus due to the cluster size cannot achieved significant threshold (Figure 3.6). However, it does not imply the thalamic activity failed to be suppressed by propofol. The propofol effect may mediated the thalamocortical interaction (Alkire et al., 2008). Indeed, the thalamocortical connectivity in default network and bilateral executive-control networks were found to be correlated with propofol-induced decrease of consciousness in previous study on this dataset (Boveroux et al., 2010). Unlike the complexity of anesthetic

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**Figure 3.7:** Conjunction map (canon2dd and sFIR) of response height differences between healthy controls and VS patients, $p < 0.05$, topo FDR correction.

**Figure 3.8:** Conjunction map of W1 minus S2 and healthy control minus VS patients in response height differences, $p < 0.05$, topo FDR correction.
action on thalamus, the obvious decrease of spontaneous hemodynamic responses in VS offer the strong empirical support that thalamus are at the heart of the neurobiology of consciousness.

3.4.1 Methodology considerations

Stimulus-evoked BOLD fMRI is one of the most conventional paradigms to investigate anesthetic influence on neuronal activation. These always only elicit specific brain regions response to task paradigm, sometime even cause unexpected or unspecific widespread BOLD signal changes on the brain. Finding a balance between complexities and applicability is always a challenge for task stimuli. Conversely, rs-fMRI is paradigm-free fMRI approaches, and allows investigating the baseline activity of the whole brain. Resting state functional connectivity analysis is the most widely used technique in these anesthesia and pathology rs-fMRI studies. Due to relatively poor temporal resolution, few studies focus on exploring the spontaneous event dynamics of anesthesia. As shown in previous works, an efficient way to reveal this spontaneous activity at cortical level from resting state BOLD signal could be through point process analysis, under the hypothesis that important features of brain dynamics at rest can be captured from relatively large fluctuations in BOLD amplitude (Tagliazucchi et al., 2012a; Wu et al., 2013a). As discussed in (Di et al., 2008), due to uncontrolled head movements during scanning, the patients with VS may show more motion artifacts than in collaborative healthy subjects. To avoid motion-related artifacts contribution to point process, 3Ddespike and aCompCor were combined to attenuate motion artifacts, to minimize the framewise relationship between head motion and signal change (Muschelli et al., 2014). To further minimize the motion artifact influence on HRF shape retrieved from point process, data scrubbing is performed (Power et al., 2012), and Mean FD power of each subject is included as a covariate for further statistical analysis (Van Dijk et al., 2012). This procedure indicates that our finding is unlikely to be due to motion artifact.

Apart from head motion artifact, relatively low signal to noise ratio (SNR) of the BOLD signal, and undesired physiological sources of variability (cardiac, pulmonary) make detection of the spontaneous point process events difficult. The GLM based HRF retrieving will benefit from heterogeneous distribution of temporal interval between these point process events, i.e. temporal jitter variation in event onset times (Buckner, 1998), while its power is relative to violation the assumption of linear additively (Boynton et al., 1996). Meanwhile, the precise estimation of HRF with sFIR model depend on the high SNR, while relatively fixed-shape canonical HRF with its derivatives model are less affected by SNR, and the temporal resolution is much better than sFIR model, which is relative to the precise of HRF parameters estimation (FWHM and time to peak). As shown in a simulation study, there is more bias in the estimates of FWHM and time to peak than response height.
Modulated spontaneous hemodynamic response to loss of consciousness

(Lindquist et al., 2009). These evidences could partially explain less group level finding discovered by sFIR model in FWHM and time to peak. Meanwhile, our findings also suggest that hemodynamic response height shows the most discriminative power than other HRF parameters. Additionally, the coupling between neural activity and the vascular response is significant in determining the amplitude and spatial resolution of the BOLD signal (Logothetis and Wandell, 2004). Regions of sparse vascularization are likely to have low efficacy of this coupling and weak or absent BOLD response. This may be related to higher hemodynamic response height found in the cortical surface.

Because resting state BOLD-fMRI is relatively easy to use, resting state HRF is methodologically simple and might substantially complement brain connectivity approach to extend our understanding of underlying mechanisms of consciousness, especially for clinical populations and conditions not suitable for PET imaging.
Point-process deconvolution of fMRI BOLD signal reveals effective connectivity alterations in chronic pain patients

Abstract

It is now recognized that important information can be extracted from the brain spontaneous activity, as exposed by recent analysis using a repertoire of computational methods. In this context a novel method, based on a blind deconvolution technique, is used to analyze potential changes due to chronic pain in the brain pain matrix’s effective connectivity. The approach is able to deconvolve the hemodynamic response function from spontaneous neural events, i.e., in the absence of explicit onset timings, and to evaluate information transfer between two regions as a joint probability of the occurrence of such spontaneous events. The method revealed that the chronic pain patients exhibit important changes in the insula’s effective connectivity which can be relevant to understand the overall impact of chronic pain on brain function.

4.1 Introduction

Recent results have shown that chronic pain is a condition that, beyond the feeling of acute pain, affects normal brain function and structure, causing cognitive impairments, including depression, sleeping disturbances and decision-making abnormalities (Apkarian et al., 2005, 2004; Baliki et al., 2008).

Disruptions and modifications in cortical dynamics due to chronic pain have been demonstrated using functional magnetic resonance imaging (fMRI), both studying activation in response to external stimulation (Derbyshire, 1999; Peyron et al., 2000) as well as using
seed based correlation analysis during the execution of simple attention demanding tasks (Baliki et al., 2008). In particular, the latter study showed for the first time that the dynamics of the default mode network (DMN) is disrupted in chronic pain.

A recent study (Baliki et al., 2012) reported that it is even possible to identify a temporal profile of brain parameters which changes during pain chronification in patients suffering sub-acute back pain. These changes involve medial prefrontal regions of the cortex, notably the insula as well as the nucleus accumbens. The insular cortex is often activated bilaterally during noxious somatosensory stimulation and has been suggested to play an important role in pain processing (Coghill et al., 1999, 1994). At the same time, the extensive connectivity of the insula suggests a multifaceted role in the dynamic of pain perception, and the need to develop new methods to unravel its complexity.

The present study uses a novel approach to detect neural events in BOLD signals to investigate the network of directed dynamical influences between brain regions involved in pain processing, in particular the insula subregions. The approach is able to deconvolve the hemodynamic response function (HRF) to spontaneous neural events, i.e., in the absence of explicit onset timings, and to evaluate information transfer between any two regions as a joint probability of the occurrence of such spontaneous events.

The paper is organized as follows: the next section describes the brain imaging data as well as the numerical methods for deconvolution and Granger causality mapping. In Section 3 the main findings are presented indicating important changes in the insula’s effective connectivity in chronic pain patients. The paper closes in Section 4 with a brief discussion on the method’s novelty as well as on the physiological relevance of the results.

4.2 Materials and methods

4.2.1 fMRI data acquisition and preprocessing

The data analyzed here correspond to 12 chronic back pain patients (CBP) (Age: 29-67 years, mean/SD=51.2/11.1; Beck depression index: 7.25±1.3; Beck anxiety index: 9.12±17; pain duration: 6.3±0.98 years [mean±SD]) and 20 healthy controls (HC) (Age: 21-60 years, mean/SD=38.4/3.43; Beck depression index: 8.96±1.3; Beck anxiety index: 7.46±1.98). All subjects were right-handed and all gave informed consent to procedures approved by Northwestern University (Chicago) IRB committee (Tagliazucchi et al., 2010). There is no significant difference in depression indices between the groups. The patients participated in an earlier study, and their clinical and demographic data, as well as pain-related parameters, have been described in (Tagliazucchi et al., 2010; Baliki et al., 2008). Participants were asked to lay still in the scanner and to keep their mind blank, eyes closed and avoid falling asleep (Fox et al., 2005). Functional magnetic resonance data was acquired using a 3T Siemens Trio whole-body scanner with echo-planar imaging capability.
using the standard radio-frequency head coil. Scanner parameters were similar to those used in an earlier study (Baliki et al., 2008). For each subject, a total of 300 images (spaced by 2.5 sec, TR) were obtained, in which the blood oxygenation level dependent (BOLD) signal was recorded for each one of the $64 \times 64 \times 49$ sites (voxels of dimension $3.4375 \text{ mm} \times 3.4375 \text{ mm} \times 3 \text{ mm}$).

Preprocessing of BOLD signal was performed using FMRIB Expert Analysis Tool (Jezzard et al., 2003). Data preprocessing included motion correction using MCFLIRT, slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal using BET, spatial smoothing using a Gaussian kernel of full-width-half-maximum 5 mm. Brain images were normalized to standard space using the MNI 152 template using FLIRT and data was resampled to $4 \text{ mm} \times 4 \text{ mm} \times 4 \text{ mm}$ resolution. A zero lag finite impulse response filter was applied to band pass filter (0.01 Hz - 0.1 Hz) the functional data (the lower frequency was chosen to avoid noise related to scanner drift and the higher frequency was chosen to eliminate high frequency artifacts related with physiological noise and head motion) (Cordes et al., 2001, 2000). An independent component analysis (ICA) de-noising procedure (Beckmann and Smith, 2004) consisting of edge removal and high frequency artifacts by linear regression was performed using Melodic.

A predefined pain matrix mask (described in Table II of (Cifre et al., 2012)) was employed in the present study, and is visualized in Figure 4.1 and as contours in Figures 4.2 and 4.3. As a control, a region with no expected pain effects, the primary visual cortex (BA 17) was used for comparison.

### 4.2.2 Spontaneous point event detection and HRF Deconvolution

Previous studies have shown that the hemodynamic processes are inhomogeneous across the whole brain (Handwerker et al., 2012a). These inhomogeneities acting over the hemodynamic response can limit the inferences of temporal precedence (Valdes-Sosa et al., 2011) which are central for establishing effective connectivity between regions. To overcome this limitation, a novel blind deconvolution technique (see Figure 4.1) was developed recently for resting-state BOLD-fMRI signals (Wu et al., 2013a). The approach relies on the idea that the resting-state BOLD spikes can be seen as the response to spontaneous neuronal events, something supported by the increasing evidence of non-random patterns governing the dynamics of the brain at rest (Tagliazucchi and Chialvo, 2011; Petridou et al., 2013).

These spontaneous events can be detected by point process analysis (PPA), picking up BOLD fluctuations of relatively large amplitude (Tagliazucchi et al., 2012a, 2010, 2011). After detecting these resting-state BOLD transients, the BOLD event onsets are stored for further reconstruction of the hemodynamic response function. The voxel-specific HRF
is obtained by fitting raw BOLD signal with triggered averages and shifted BOLD event onsets, in order to finally recover signals at the neural level by Wiener deconvolution (Glover, 1999).

To characterize the hemodynamic response function elicited by spontaneous point events, two easily interpretable parameters of the HRF which estimate the potential changes in neuronal activity (Lindquist and Wager, 2007) were calculated: the response height and the time to peak.

### 4.2.3 Granger Causality mapping

To explore the large scale directional interactions between insula and neuronal assemblies in other cortical regions of pain matrix, Granger causality (GC) analysis is applied on the deconvolved BOLD-fMRI data. Here we provide a brief introduction to GC. Given \( k \) covariance-stationary variables \( \{x_i(t)\}_{i=1,...,k} \), the state vectors are denoted \( X_\alpha(t) = (x_\alpha(t-m), \cdots, x_\alpha(t-1)) \), \( m \) being the model order. Let \( \epsilon(x_\alpha|Y) \) be the mean squared error prediction of \( x_\alpha \) on the basis of the vectors \( Y \). The Granger causality index from \( \beta \in \mathbb{R}^{N\times1} \) to \( \alpha \in \mathbb{R}^{N\times1} \) is defined as follows:

\[
c(\beta \rightarrow \alpha) = \log \frac{\epsilon(x_\alpha|X_\beta)}{\epsilon(x_\alpha|X_\alpha \cup X_\beta)} \tag{4.1}
\]

in addition, for further statistical analysis, GC value \( c \) is transformed into \( c' = \sqrt{n \cdot c - (m - 1)/3} \), which is considered to be approximately normal (where \( n = N - m \). If \( c = 0 \), \( n \cdot c \sim \chi^2(m) \)) (Geweke, 1982).
Figure 4.2: Significant differences in the HRF parameters between chronic pain patients versus the control group. Top panels represent the response height and the bottom panels the latency to the peak of the response. Voxels depicted overlaid on the anatomical image are those which passed Alphasim correction with $p < 0.05$. The purple contour lines indicate the location of the voxels belonging to the pain matrix.
Figure 4.3: Granger Causality mapping between the Insula and the entire pain matrix. Results illustrate the significant differences between the Granger Causality maps of the patients versus the control group. Voxels depicted, overlaid on the anatomical images, are those passing Alphasim correction with $p < 0.05$. As in Figure 4.2, the pain matrix is indicated by the purple contour lines.

The model order used in this study is $m = 1$, evaluated by leave-one-out cross-validation, and common in fMRI GC studies (Roebroeck et al., 2005). Regression models were estimated by the ordinary least squares algorithm.

Finally, pairwise causal interaction was investigated by mapping the influence between the seed ROI of bilateral insula and the deconvolved BOLD time series of the individual voxels belonging to the entire pain matrix (see above).
4.2.4 Statistical Analysis

To compute the group differences (i.e., patient vs. control groups) on pain matrix at voxelwise level, a two-sample T-test was implemented in SPM8, independently for HRF parameters and seed based GC mapping. Statistical significance was estimated via a Monte Carlo simulation (Alphasim). A cluster-wise threshold of $p < 0.05$ by combining a $p < 0.04$ individual voxel threshold and different minimum cluster size of $k$ contiguous voxels, corrected for multiple comparisons (implemented in the REST toolbox, www.restfmri.net; Gaussian filter width was estimated from each SPM T-map, and $k$ varied with Gaussian filter width; cluster connection radius 5 mm, and 1000 iterations).

4.3 Results

4.3.1 Spontaneous hemodynamic response

Figure 4.2 summarizes the main findings concerning the parameters of spontaneous BOLD activity. It is seen that in terms of the HRF’s time to peak (compared to the control subjects) patients response function was characterized by longer time to peak latency in precentral and postcentral gyrus, but shorter time to peak latency in anterior cingulate, posterior cingulate, medial frontal gyrus, dorsal anterior cingulate cortex (dACC), orbitofrontal cortex (OFC), precuneus (PCUN) and retrosplenial cingulate cortex (RSC) (see bottom panel of Figure 4.2).

Concerning the other parameter, the HRF response height, the major modifications were found predominately in the insula. Other regions included putamen, superior temporal gyrus, parahippocampal gyrus, caudate and amygdala (AMG)(see top panel of Figure 4.2). As a control we looked at the same quantities in the primary visual cortex V1, a region not involved in pain processing, finding no significant difference between groups.

4.3.2 Seed-based Granger causality mapping

To compute the effective connectivity mapping of the insula, we selected seeds ROIs based on the two sample t-test results of the hemodynamic responses. They were centered at the two peaks T-values (response height) inside the bilateral insular regions (MNI coordinates: left ventral posterior insula (l-vPI), [-40 -4 -4]; right dorsal anterior insula (r-dAI), [32 20 8]; with sphere 8mm diameter). GC mapping was then independently implemented for these two subregions of the insula.

The GC mapping between left vPI and the following regions exhibited lower information transfer, both incoming and outgoing, for patients: medial frontal gyrus, precentral gyrus, postcentral gyrus, premotor cortex (BA6), supplementary motor area (SMA), paracentral lobule (PCL), primary motor cortex (BA4), primary somatosensory cortex (BA3,1&2).
Table 4.1: Significant results of HRF parameters/Granger causality mapping resulting from the comparison between the patient and the control groups. Abbreviations: C. size: Cluster size; Res. Height: Response Height; Time to Peak: Time to Peak response; In, l-vPI: Incoming network, Left vPI; Out, l-vPI: Outgoing network, Left vPI; Out, r-dAI: Outgoing network, Right dAI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Brain region</th>
<th>BA</th>
<th>C. size</th>
<th>peak MNI (x,y,z)</th>
<th>peak T value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resp. Height</td>
<td>Temporal Sup L</td>
<td>-</td>
<td>116</td>
<td>-44 -4 -8</td>
<td>3.42</td>
</tr>
<tr>
<td></td>
<td>Hippocampus R</td>
<td>-</td>
<td>124</td>
<td>20 -8 -16</td>
<td>3.01</td>
</tr>
<tr>
<td>Time to Peak</td>
<td>Postcentral L</td>
<td>-</td>
<td>62</td>
<td>-32 -28 72</td>
<td>3.97</td>
</tr>
<tr>
<td></td>
<td>Rectus L</td>
<td>11</td>
<td>78</td>
<td>-4 44 -16</td>
<td>-4.09</td>
</tr>
<tr>
<td></td>
<td>Vermis 4 5</td>
<td>-</td>
<td>52</td>
<td>4 -48 4</td>
<td>-4.64</td>
</tr>
<tr>
<td>In, l-vPI</td>
<td>SMA R</td>
<td>-</td>
<td>215</td>
<td>12 -8 56</td>
<td>-2.92</td>
</tr>
<tr>
<td>Out, l-vPI</td>
<td>PCL R</td>
<td>-</td>
<td>445</td>
<td>8 -28 80</td>
<td>-3.57</td>
</tr>
<tr>
<td>Out, r-dAI</td>
<td>PCL R</td>
<td>-</td>
<td>166</td>
<td>8 -28 80</td>
<td>-3.93</td>
</tr>
</tbody>
</table>

For the case of the right dAI it was found that there is significantly less information transfer for voxels located in: premotor cortex, superior frontal gyrus, supplementary motor area, medial frontal gyrus, paracentral lobule, precentral gyrus, postcentral gyrus. No significant difference in the effective connectivity was reported from the pain matrix to right dAI.

The results are presented in figure 4.3 and summarized in table 4.1.

### 4.3.3 Joint probabilities of neural events

To further characterize the causal effects from and to the insula, and to demonstrate how instantaneous neural events detected in the BOLD signal can be not only helpful for deconvolution, but can even reveal themselves this causal effects, we investigated the relative timing of the onset of the neural events in the paracentral right lobule (see table 4.1) with respect to those occurring in the left vPI.

Every time that an event was detected in the time series of a voxel belonging to the paracentral right lobule, we searched for other events occurring in the left vPI \([-L, L]\] centered at the onset, where \(L = 3\) TR. These co-occurring events were accumulated in time for each spatial location, defining in this way the joint distribution probability reported in Figure 4.4. Thus this distribution describes how events in the left vPI trigger events in the paracentral right lobule (positive lags) or vice-versa (negative lags). The distributions in the patient and control groups are compared with randomized cases in which the timing of the onsets in the Insula were randomized (on 500 trials), preserving the original values of the inter-events times (Figure 4.4). These distributions confirm the decreased influence in both direction found by GC analysis.
4.4 Discussion

The present study proposes a novel data-driven approach to map the altered patterns on effective connectivity of insular subregions in chronic back pain patients. The results demonstrate a dissociation in the pain information integration profiles of posterior and anterior insula, which has not been emphasized in the prior literature. The joint probabilities of neural events method allow us to identify precise time lag distribution of causal interactions between the source and target regions.

The insular cortex is a functionally and cytoarchitectonically diverse region, exhibiting extensive anatomical connectivity to sensory regions, as well as to higher cognitive brain areas. Plenty of neuroimaging studies have explicitly investigated functional differences across subregions of the insula. Posterior insula (PI) was found to be functionally connected to primary and secondary motor and somatosensory cortices; additionally it conveys pain information and is a critical site for interoception (Craig, 2002). Accumulated evidences also suggests that dorsal anterior insula (AI) is functionally connected to the cognitive control network, might play a general role in negative affect processes, and correlate to empathy for pain (Bernhardt et al., 2013; Deen et al., 2011). In the current study, we evaluated the parameters of the hemodynamic response at rest to detect pain sensitive subregion of the insula: l-vPI and r-dAI, then explored the pain processing pathway of information transmission in the insula, such as somatosensory/interoceptive information from PI or affective information from vAI influence pain perception and pain-related
behavior.
Reduced information transfer to and from the insula in chronic back pain is thus an indicator of how this region loses part of its potential as a hub for information processing. The prominence of this effect to and from somatosensory and motor areas suggests that long term pain itself could modify motor behavior, (i.e. patients exercise less and differently from healthy subjects), and consequently the dynamics of these regions, as afferents and efferents.
The present results add to a large body of evidence indicating that chronic pain involves dynamical changes that affects normal brain function which in turn can impair cognitive function, including depression, sleeping disturbances and decision-making abnormalities (Apkarian et al., 2005, 2004; Baliki et al., 2008).
The approach used here is derived from two lines of work that together allows for a novel view of the changes in brain dynamical connectivity. On one side it adds strength to the previous suggestions (Tagliazucchi et al., 2012a, 2010, 2011; Wu et al., 2013a) that a few (relatively large) BOLD events can contain substantial information to describe functional connectivity. On the other side, the seed based Granger causality mapping allows the precise description of the effective connectivity at a fine scale.
The changes in the effective connectivity described in the results section are fully consistent with the current data (Apkarian et al., 2009) validating the novel methodology and encouraging a more detailed analysis of other regions of interest described recently (Baliki et al., 2012) as involved in the transition from acute to chronic pain.
It should be pointed out that the long TRs may affect the precision and robustness in the evaluation of HRF and Granger causality mapping. Consequently, further studies with more convenient imaging parameters would be necessary in order to investigate more closely the distinct and hemispherical patterns of large-scale effective connectivity of all insular subregions, and the link with pain magnitude. Effects of age on metabolism and consequently on HRF are controversial (Gauthier et al., 2013; Peng et al., 2014). We cannot exclude that the age difference between groups could have had an impact on the present results. Nonetheless age itself could not explain the localization of significant differences in the HRF shape in subregions of the pain matrix.
In summary, we have shown that by deconvolving the hemodynamic response function to spontaneous neural events it can be demonstrated via Granger causality that chronic pain patients display important changes in effective connectivity to and from subregions of the insula, mainly involving sensorimotor areas; these changes are flanked by modification to the shape of the HRF in the pain matrix.
Decomposition of the Transfer Entropy: Partial Conditioning and Informative Clustering

Abstract

We propose a formal expansion of the transfer entropy to address the problem of partial conditioning evaluating information flow in multivariate datasets. This approach will then be adapted to put in evidence irreducible sets of variables which provide information for the future state of each assigned target. Multiplets characterized by a high value will be associated to informational circuits present in the system, with an informational character (synergetic or redundant) which can be associated to the sign of the contribution. These methods are then applied to the analysis of fMRI data.

5.1 Introduction

The scope of this work is to get the maximum information on the structure and function of dynamical networks, adapting existing analysis tools to short and noisy time series and exploiting the redundancy naturally present in the data as an extra feature.

A great need exists for the development of effective methods of inferring network structure from time series data, in particular in neuroscience: determining how the brain is connected is crucial in order to understand how it works.

Granger causality has become one of the methods of choice to determine whether and how two time series exert causal influences on each other (Bressler and Seth, 2011). This approach is based on prediction: if the prediction error of the first time series is reduced by including measurements from the second one in the linear regression model, then the
second time series is said to have a causal influence on the first one.

From the beginning (Granger, 1969; Wiener, 1956), it has been known that if two signals are influenced by a third one that is not included in the regressions, this leads to spurious causalities, so an extension to the multivariate case is in order. The conditional Granger causality analysis (CGCA) (Geweke, 1984) is based on a straightforward expansion of the autoregressive model to a general multivariate case including all measured variables.

Often though, a fully multivariate approach can present problems which can be both computational and conceptual, ranging from high running time to degeneration into the curse of dimensionality and wrong information flow detection due to the presence of redundancy.

A typical case study in which the above problems emerge dramatically, is when one wants to infer connectivity in functional Magnetic Resonance Imaging (fMRI) data. This work is dedicated to address both issues in two related but complementary frameworks:

- Partial conditioning of information flow measures to a limited subset of variables.
- Characterizing network structure by identifying, from each target variable, the subgroups of variables which are redundant or synergetic for it.

A crucial point in all these approaches is to exploit the connection between Granger causality and information-theoretic approaches like the transfer entropy introduced in (Schreiber, 2000), which have been shown to be equivalent for Gaussian variables (Barnett et al., 2009), and also for other probability densities (Hlaváčková-Schindler, 2011). Hence, from the conceptual point of view a weighted network obtained by Granger causality analysis can be given an interpretation in terms of flow of information between different components of a system. Furthermore, entropy based measures allow approaches such as partial decomposition and separation of state-dependent contributions.

### 5.2 Methods

#### 5.2.1 Partial Conditioning

Marinazzo et al. have recently addressed the problem of partial conditioning to a limited subset of variables (Marinazzo et al., 2012), in the framework of information theory and we have shown that conditioning on a small number of variables could be sufficient to remove indirect interactions if the connectivity pattern is sparse. This subgroup of variables may be chosen as the most informative for the driver variable.

We recall here briefly the main ideas of this approach.

Let us consider $n$ time series $\{x_{\alpha}(t)\}_{\alpha=1,\ldots,n}$; the state vectors are denoted

$$X_{\alpha}(t) = (x_{\alpha}(t-m), \ldots, x_{\alpha}(t-1)),$$
Partial Decomposition of the Transfer Entropy

$m$ being the window length (the choice of $m$ can be done using the standard cross-validation scheme), and imagine that we want to evaluate the information flow $\beta \rightarrow \alpha$; we fix the number of variables, to be used for conditioning, equal to $n_d$. We denote $Z = (X_{i_1}, \ldots, X_{i_{n_d}})$ the set of the $n_d$ variables, in $X \setminus X_\beta$, most informative for $X_\beta$. In other words, $Z$ maximizes the mutual information $I\{X_\beta; Z\}$ among all the subsets $Z$ of $n_d$ variables. Then, we evaluate the causality

$$c(\beta \rightarrow \alpha) = \log \frac{\epsilon(x_\alpha|Z)}{\epsilon(x_\alpha|Z \cup X_\beta)}.$$ (5.1)

Under the Gaussian assumption, the mutual information $I\{X_\beta; Z\}$ can be easily evaluated, see (Barnett et al., 2009). Moreover, instead of searching among all the subsets of $n_d$ variables, we adopt the following approximate strategy. Firstly the mutual information of the driver variable, and each of the other variables, is estimated, in order to choose the first variable of the subset. The second variable of the subsets is selected among the remaining ones, as those that, jointly with the previously chosen variable, maximizes the mutual information with the driver variable. Then, one keeps adding the rest of the variables by iterating this procedure. Calling $Z_{k-1}$ the selected set of $k - 1$ variables, the set $Z_k$ is obtained adding, to $Z_{k-1}$, the variable, among the remaining ones, with greatest information gain. This is repeated until $n_d$ variables are selected. This greedy algorithm, for the selection of relevant variables, is expected to give good results under the assumption of sparseness of the connectivity.

### 5.2.2 Expansion of the Transfer Entropy to Identify Subgraphs

Information theoretic treatment of groups of correlated degrees of freedom can reveal their functional roles as memory structures or those capable of processing information (Borst and Theunissen, 1999). Information quantities reveal if a group of variables may be mutually redundant or synergetic (Schneidman et al., 2003; Bettencourt et al., 2007). The application of these insights to identify functional connectivity structure is a promising line of research. An approach to identify functional subgraphs in complex networks, relying on an exact expansion of the mutual information with a group of variables, has been presented in (Bettencourt et al., 2008).

Here we propose a formal expansion of the transfer entropy to put in evidence irreducible sets of variables which provide information for the state of the target. Multiplets characterized by an high value, unjustifiable by chance, will be associated to informational circuits present in the system, with an informational character (synergetic or redundant) which can be associated to the sign of the contribution.

We start describing the work in (Bettencourt et al., 2008). Given a stochastic variable $X$ and a family of stochastic variables $\{Y_k\}_{k=1}^n$, the following expansion for the mutual
Partial Decomposition of the Transfer Entropy

Information has been derived there:

\[ S(X|\{Y\}) - S(X) = -I(X; \{Y\}) = \]
\[ = \sum_i \frac{\Delta S(X)}{\Delta Y_i} + \sum_{i>j} \frac{\Delta^2 S(X)}{\Delta Y_i \Delta Y_j} + \cdots + \frac{\Delta^n S(X)}{\Delta Y_1 \cdots \Delta Y_n}, \quad (5.2) \]

where the variational operators are defined as

\[ \frac{\Delta S(X)}{\Delta Y_i} = S(X|Y_i) - S(X) = -I(X; Y_i), \quad (5.3) \]

\[ \frac{\Delta^2 S(X)}{\Delta Y_i \Delta Y_j} = -\Delta I(X; Y_i|Y_j) = I(X; Y_j) - I(X; Y_i|Y_j), \quad (5.4) \]

and so on.

Now, let us consider \( n + 1 \) time series \( \{x_\alpha(t)\}_{\alpha=0,...,n} \). The lagged state vectors are denoted

\[ Y_\alpha(t) = (x_\alpha(t-m), \ldots, x_\alpha(t-1)), \]

\( m \) being the window length.

Firstly we may use the expansion (5.2) to model the statistical dependencies among the \( x \) variables at equal times. We take \( x_0 \) as the target time series, and the first terms of the expansion are

\[ W^0_i = -I(x_0; x_i) \quad (5.5) \]

for the first order;

\[ Z^0_{ij} = I(x_0; x_i) - I(x_0; x_i|x_j) \quad (5.6) \]

for the second order; and so on.

Here we propose to consider also

\[ S(x_0|\{Y_k\}_{k=1}^n) - S(x_0) = -I(x_0; \{Y_k\}_{k=1}^n), \quad (5.7) \]

which measures to what extent the remaining variables contribute to specifying the future state of \( x_0 \). This quantity can be expanded according to (5.2):

\[ S(x_0|\{Y_k\}_{k=1}^n) - S(x_0) = \sum_i \frac{\Delta S(x_0)}{\Delta Y_i} + \sum_{i>j} \frac{\Delta^2 S(x_0)}{\Delta Y_i \Delta Y_j} + \cdots + \frac{\Delta^n S(x_0)}{\Delta Y_1 \cdots \Delta Y_n}. \quad (5.8) \]

A drawback of the expansion above is that it does not remove shared information due to common history and input signals; therefore we propose to condition on the past of \( x_0 \), i.e.
Y₀. To this aim we introduce the conditioning operator \( C_{Y₀} \):

\[
C_{Y₀}S(X) = S(X|Y₀),
\]

and observe that \( C_{Y₀} \) and the variational operators (5.3) commute. It follows that we can condition the expansion (5.8) term by term, thus obtaining

\[
S(x₀|\{Y_k\}_{k=1}^n|Y₀) - S(x₀|Y₀) = -I(x₀; \{Y\}_{k=1}^n|Y₀) = \sum_i \frac{\Delta S(x₀|Y₀)}{\Delta Y_i} + \sum_{i>j} \frac{\Delta^2 S(x₀|Y₀)}{\Delta Y_i \Delta Y_j} + \cdots + \frac{\Delta^n S(x₀|Y₀)}{\Delta Y_i \cdots \Delta Y_n}.
\]

(5.9)

We note that variations at every order in (5.9) are symmetrical under permutations of the \( Y_i \). Moreover statistical independence among any of the \( Y_i \) results in vanishing contribution to that order: each nonvanishing term in this expansion accounts for an irreducible set of variables providing information for the specification of the target. The first order terms in the expansion are given by:

\[
A_{i}^0 = \frac{\Delta S(x₀|Y₀)}{\Delta Y_i} = -I(x₀; Y_i|Y₀),
\]

(5.10)

and coincide with the bivariate transfer entropies \( i \to 0 \) (times -1). The second order terms are

\[
B_{ij}^0 = I(x₀; Y_i|Y₀) - I(x₀; Y_i|Y_j, Y₀),
\]

(5.11)

whilst the third order terms are

\[
C_{ijk}^0 = I(x₀; Y_i|Y_j, Y₀) + I(x₀; Y_i|Y_k, Y₀) - I(x₀; Y_i|Y₀) - I(x₀; Y_i|Y_j, Y_k, Y₀).
\]

(5.12)

An important property of (5.9) is that the sign of nonvanishing terms reveals the informational character of the corresponding set of variables: a negative sign indicates that the group of variables contribute with more information, than the sum of its subgroups, to the state of the target (synergy), while positive contributions correspond to redundancy. Significant terms in the proposed expansion correspond to irreducible sets of variables which provide information for the future state of the target channel. Being the exhaustive search, in the set of all the subsets of the variables at hand, unfeasible, we limited our analysis to sets of four variables. In order to look for larger multiplets, we implemented an approximate strategy, based on a greedy search. Starting from a redundant (synergetic) multiplet of two variables, selected as those which have an informational contribution significantly higher than the one obtained reshuffling the time series, another variable is selected among the remaining ones, as the one that, jointly with the previously chosen variable, leads to the most redundant (synergetic) multiplet of five variables. Then, one keeps adding more and more variables by iterating this procedure, until no significantly
increase of redundancy (synergy) is observed adding any of the remaining variables.

5.3 Application to fMRI data

We used two resting state datasets from a public repository. Data were acquired by using of single-shot gradient echo planar imaging (EPI) sequence (repetition time [TR]: 2000 ms and 1400 ms; echo time: 30 ms; slices: 33; thickness: 3 mm; gap: 0.6 mm; field of view: 200 × 200 mm²; in-plane resolution: 64 × 64; flip angle: 90°). Preprocessing of resting-state images was performed using the Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm), including slice-timing corrected relative to middle axial slice for the temporal difference in acquisition among different slices, realigned with the corresponding 3-D structure image, head motion correction (for all subjects, the translational or rotational parameters of a data set did not exceed ±1 mm or ±1°), spatial normalization into a standard stereotaxic space, parameters from normalizing 3-D structure images to the Montreal Neurological Institute T1 template in SPM8 were written to fMRI images then resampled to 3-mm isotropic voxels. The functional images were segmented into 90 regions of interest (ROIs) using automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002). For each subject, the representative time series of each ROI was obtained by averaging the fMRI time series across all voxels in the ROI. Several procedures were used to remove possible spurious variances from the data through linear regression. These were 1) six head motion parameters obtained in the realigning step, 2) signal from a region in cerebrospinal fluid, 3) signal from a region centered in the white matter, 4) global signal averaged over the whole brain. The hemodynamic response function was deconvolved from the BOLD time series.

5.3.1 Partial Decomposition

In order to select the variables over which conditioning, in figure 5.1 we plot the mutual information gain as a function of the number of variables included $n_d$: as expected it decreases as $n_d$ increases. The curves correspond to three different standard templates used to average the voxels. Interestingly all the curves start to become flatter around $n_d = 6$, irrespective of the number of total variables (17, 90 or 160). This phenomenon could be explained considering that multivariate analysis by hierarchical clustering and multidimensional scaling consistently defined six major systems in the resting brain (Salvador et al., 2005).

1http://www.nitrc.org/projects/fcon_1000/
Figure 5.1: The mutual information gain, when the \((n_d + 1)\)-th variable is included, is plotted versus \(n_d\) for datasets obtained using three different templates averaging the voxels over 17, 90 or 160 regions.

5.3.2 Information Subgraphs

We start reporting in figure 5.2 the histograms from the first three order terms, computed exactly, confronted with the results obtained by reshuffling the time series. We can observe, in the graph of the third order, that redundant and synergetic contributions seem to have different probability distributions.

Coming to the greedy decomposition, a convenient way to visualize the results is to count, for a given target, how many times another variable appears in redundant or synergetic multiplets. In figure 5.3 we report these findings for the left precuneus, which has been previously reported as a sink hub (mostly receiving information from other brain regions) (Cavanna and Trimble, 2006). From the figure is evident the balance between functional segregation and integration in the brain.
Figure 5.2: Distribution of the first three order terms in the decomposition of the transfer entropy the resting state fMRI. The results are confronted with those obtained reshuffling the time series. Left: first order; Center: second order; Right: third order.
**Figure 5.3:** Most redundant regions for left precuneus. The size of the regions is proportional to the number of times that the region is present in a redundant multiplet. The color corresponds to each of the six subsystems of the resting brain (Brown: Medial Temporal, Light Blue: Subcortical, Green: Occipital, Dark Blue: Frontal, Purple: Temporal, Red: Parietal-(Pre)motor.)
CHAPTER 6

DynamicBC: A MATLAB Toolbox for Dynamic Brain Connectome Analysis

Abstract

The brain connectome collects the complex network architectures, looking at both static and dynamic functional connectivity. The former normally requires stationary signals and connections. However, the human brain activity and connections are most likely time dependent and dynamic, and related to ongoing rhythmic activity. We developed an open-source MATLAB toolbox DynamicBC with user-friendly graphical user interfaces, implementing both dynamic functional and effective connectivity for tracking brain dynamics from functional MRI. We provided two strategies for dynamic analysis: 1) the commonly utilized sliding-window analysis and 2) the flexible least squares based time-varying parameter regression strategy. The toolbox also implements multiple functional measures including seed-to-voxel analysis, region of interest (ROI)-to-ROI analysis, and voxel-to-voxel analysis. We describe the principles of the implemented algorithms, and then present representative results from simulations and empirical data applications. We believe that this toolbox will help neuroscientists and neurologists to map easily dynamic brain connectomics.

6.1 Introduction

The brain connectome collects network architectures. At macroscopic scales, the human brain connectomics provide a comprehensive description of the anatomical pathways and functional interactions among distinct brain areas (Sporns, 2014, 2013). The structural
connectomics essentially comprises a comprehensive map of the anatomical connections reflecting axonal pathways (Sporns et al., 2005), and the structural covariance connectivity interpreted as the phenotype of brain development and/or plasticity (He et al., 2007; Alexander-Bloch et al., 2013). Additionally, the functional connectomics can be captured as patterns of functional covariance network (Liao et al., 2013b; Zhang et al., 2011), functional and effective connectivity networks (Friston, 2009, 2011; Marinazzo et al., 2011; Wu et al., 2013a; Marinazzo et al., 2014).

Functional connectivity (FC) measures statistical patterns of interactions among remote brain regions; while effective connectivity (EC) discerns the transfer of information such as directed causal interactions (Friston, 1994; Rubinov and Sporns, 2010). Consequently, the brain can be seen as a large-scale functional integrated network both during cognitive tasks and at resting state (Bressler and Menon, 2010). Resting-state FC represents the synchronization of spontaneous blood-oxygenation level-dependent (BOLD) activity and is typically analyzed in terms of correlation, coherence, and spatial grouping based on temporal similarities (Biswal et al., 1995; Beckmann et al., 2005; van den Heuvel et al., 2008). These FC analyses always assume that the functional connections remain constant during the whole period of data collection.

However, both emerging theoretical ideas and empirical observations suggest that the human brain connectome is most likely to be time dependent and dynamic, and to be related to ongoing rhythmic activity (Sporns, 2011). The functional repertoire of brain connectome is continually revisited and rehearsed in endogenous neural activity (Deco and Corbetta, 2011). Recent empirical human, macaque, and rat studies have observed the phenomenon that brain functional connectivity can indeed exhibit non stationary activity, and change over a short time (Chang and Glover, 2010; de Pasquale et al., 2010; Kang et al., 2011; Handwerker et al., 2012b; Di and Biswal, 2013; Hutchison et al., 2013; Lee et al., 2013a; Allen et al., 2014), and even across a few spontaneous points (Tagliazucchi et al., 2012a; Liu and Duyn, 2013; Wu et al., 2013a). Hence, dynamic techniques track the variability of the topology of the brain connectome across different cognitive states (Bassett et al., 2011; Fornito et al., 2012) and the evolution of diseased brain networks (Liao et al., 2013a; Zhang et al., 2014b).

Several modeling strategies have been developed to meet brain dynamics need (Hutchison et al., 2013). The most commonly utilized approach, called sliding-window analysis, is performed by conducting functional connectivity on a set number of data points. Much earlier defined paradigms information or stationary assumptions regarding the signal must be made prior to its calculation. Another widely used data-driven approach, such as Kalman filtering (KF), is capable of assessing rapidly changing connectivity relationships between brain areas (Kang et al., 2011).

Recently, several advanced toolboxes providing indexes of dynamic brain connectivity have been developed, such as GIFT (http://mialab.mrn.org/software/gift/) (Allen
et al., 2014), eConnectome (http://econnectome.umn.edu) (He et al., 2011), BSMART (www.brain-smart.org/) (Cui et al., 2008). However, most of them either focus on a special modality (e.g., fMRI, EEG, MEG) and/or include only a subset of measures as part of a more general-purpose toolbox. More important, tracking dynamic FC and EC extends the repertoire of brain connectome. However, it is still desired that a unified toolbox facilitate the neuroscientists and neurologist to map dynamic brain connectome easily.

We hereby developed a publicly available toolbox named DynamicBC (dynamic brain connectome toolbox) (www.restfmri.net/forum/DynamicBC). It is an open-source MATLAB toolbox with user-friendly graphical user interfaces (GUI). The toolbox supports NIfTI and ANALYZE images (*.nii and *.img) that would be preprocessed in the REST (Song et al., 2011) and the DPARSF (Chao-Gan and Yu-Feng, 2010) toolkit, as well as ASCII and .mat formats. The DynamicBC implements both dynamic FC and EC for tracking brain dynamics from functional MRI (fMRI). Particularly, a distribution-free time-varying parameter regression strategy was implemented. In addition, multiple region of interest (ROI) setting ways are provided, e.g., seed-to-voxel, ROI-to-ROI and voxel-to-voxel. In the following section, the remainder of this work first describes the principles of the algorithms implemented, and then we present representative results from simulations and real data, to illustrate the reliability of all these dynamic connectivity measures.

6.2 Function Module Implemented in DynamicBC

6.2.1 Overview of usage of the toolbox

The DynamicBC was developed by cross platform MATLAB (Mathworks, Inc.) programming language, with a user-friendly GUI, under a 64-bit Windows environment. It is integrated by the modules of connectivity types, dynamic analysis strategies, and ROI set (Fig. 6.1).

6.2.2 Connectivity Types Selection

Functional Connectivity

The toolbox focuses on the Pearson linear correlation to measure the FC between pair of regions:

\[ r_{xy} = \frac{\sum_{t=1}^{T} [x(t) - \bar{x}] [y(t) - \bar{y}]}{TS_x S_y} \]

(6.1)

where \( r_{xy} \) is the Pearson correlation coefficient, \( x(t) \) and \( y(t) \) are the seed and target variables with means \( \bar{x} \) and \( \bar{y} \), and standard deviations \( S_x \) and \( S_y \), respectively. The summation limit, \( T \), corresponds to the total number of time points. The most resting-
Figure 6.1: The framework of the DynamicBC toolbox. A graphical user interface (GUI) can be started by calling the 'DynamicBC' function in the command window of the MATLAB. The following procedures include three parts: selection of connectivity types (the functional and effective connectivity), selection of dynamic analysis strategies (the sliding-window and flexible least squares (FLS), and the selection of connectivity measures (the seed-to-voxel, ROI-to-ROI, and voxel-to-voxel analysis). The subsequent brain connectomes are then visualized.

State fMRI studies used this Pearson linear correlation with full-length time series, referred to as static FC (s-FC) (Biswal et al., 1995; Fox et al., 2005; Fransson, 2005; Zuo et al., 2012).

Effective Connectivity

The bivariate Granger causality (GC) to explore EC was employed in the current toolbox, which tested the null hypothesis that region $x$ does not Granger-cause region $y$ measured via linear autoregressive model. The GC index from $x$ to $y$ is defined as follows:

$$F_{x \rightarrow y} = \ln \frac{\sum (\xi_t)}{\sum (\eta_t)}$$

(6.2)
where $\xi_t$ and $\eta_t$ are the residuals of the restricted and unrestricted regression models respectively, and $\Sigma$ indicates the variance. The static EC (s-EC) was termed to describe GC relationship by full-length time series.

### 6.2.3 Dynamic Analysis Strategies

To describe the dynamic connectivity among the brain areas, we employed a time-varying parameter regression method, which is briefly described as follows:

$$y(t) = x(t)\beta(t) + u(t)$$

(6.3)

where $x(t)$ and $y(t)$ are the seed and target variables respectively, and $u(t)$ is the approximation error, and $\beta(t)$ is the coefficient to determine whether two variables covary and reflect the dynamic connectivity between $x$ and $y$ at time $t$.

#### Sliding-window Analysis

If we treat $x$ and $y$ in a short time window as being generated by an underlying (approximately) and stationary stochastic process, then the model has constant parameters during this short period. Furthermore, if the values of $x$ and $y$ are normally distributed and homoscedastic, coefficient $\beta = r_{xy}\frac{\Sigma_x}{\Sigma_y}$ can be estimated by ordinary least squares estimate in a short time window. Here we employ $r_{xy}$ as the strength of dynamic FC (d-FC) in the short time window, without considering of the scaling in samples. By transforming equation 6.3 into the vector autoregressive model, and following a similar procedure, the time-varying GC between $x$ and $y$ could be evaluated by means of sliding-window analysis.

#### Flexible Least Squares

The value of $\beta(t)$ may continuously change for various reasons. For example, switching in different tasks, or could be the consequence of underlying physiological process. There are two approaches to estimate the continuous changed model parameters at each observation. One popular methodology is the application of the Kalman filtering (KF) to infer time-varying parameters (Kalman, 1960). Another tool is the Flexible Least Squares (FLS) (Kalaba and Tesfatsion, 1989; Hastie and Tibshirani, 1993). The KF typically builds on the assumption of a certain distribution in the innovations (which is usually set to be normal distribution), while FLS is distribution-free. Here we only focus on the distribution-free method. The idea of the FLS method is to assign two types of residual error to each possible coefficient sequence estimate. The first one is the sum of squared residual measurement errors:

$$r^2_M(\beta, T) = \sum_{t=1}^{T} (y(t) - x(t)\beta(t))^2$$

(6.4)
matching the prior measurement specification: \( y(t) - x(t)\beta(t) \approx 0 \). The other is the sum of squared residual dynamic error, in which FLS declares that the vector of coefficients evolves slowly over time \( (\beta(t + 1) - \beta(t)) \approx 0 \), formally:

\[
r^2_D(\beta, T) = \sum_{t=1}^{T} (\beta(t + 1) - \beta(t))^T (\beta(t + 1) - \beta(t))
\]

(6.5)

with a given \( \mu \) weighting parameter, Kalaba and Tesfatsion (Kalaba and Tesfatsion, 1989) define the incompatibility cost assigned to any \( \beta \) coefficient sequence as

\[
C(\beta, \mu, T) = \mu \ldots r^2_D + r^2_M(\beta, T)
\]

(6.6)

The incompatibility cost function \( C(\beta, \mu, T) \) generalizes the goodness-of-fit criterion function for ordinary least squares estimation by permitting the coefficient vector \( \beta(t) \) to vary over time. When \( \mu \) approaches was set to zero, \( r^2_M \) can generally be brought down close to zero and the corresponding value for \( r^2_D \) will be relatively large, resulting in a rather erratic sequence of estimates. As \( \mu \) becomes arbitrarily large, the incompatibility cost function assigns all importance to the dynamic specification. This case yields the ordinary least squares solution, \( r^2_M \) is minimized subject to the following formula: \( r^2_D = 0 \).

6.2.4 ROI Set for Dynamic FC and EC

The implementation includes three ways to set ROI for dynamic brain connectivity analysis (see Fig. 6.1). Seed-to-voxel (voxel wise) analysis calculated the bivariate FC/EC between seed brain region and every voxel in the whole brain. ROI-to-ROI (ROI-wise) analysis computed the bivariate FC/EC between each pair of ROIs, resulting brain connectivity matrix (network) allows users to further perform graph theoretical analysis (Liao et al., 2010; Wu et al., 2013b). Voxel-to-voxel computed the bivariate FC/EC between every pair of voxels without using a priori seed/ROI to mapping whole-brain connectome (Tomasi and Volkow, 2010; Zuo et al., 2012). In addition, the toolbox then provides the functional connectivity degree (FCD) that counts total number of connections of a given voxel, while the functional/effective connectivity strength (FCS/ECS) that sums of weights of all the connections of a given voxel. Only functional/effective connectivity value of given voxel above a predefined threshold (corresponding P value or family-wise error corrected P value) were counted or summed.
6.3 Illustrations of Dynamic Brain Connectome

6.3.1 Simulation

The following simulated example is explored here to validate the reliability of uncovering dynamic FC by short sliding-window analysis and FLS, as well as the KF analysis were included.

\[
\begin{align*}
  y &= x_1 \beta_1 + x_2 \beta_2 + \epsilon \\
  \beta_1 &= 0, x_1(t) = \epsilon_1(t), \text{ if } t \in [1:50], [101:150], [201:250] \\
  \beta_1(t) &= \log(10t), x_1(t) = \sin(t + 10) + 0.01, \text{ if } t \in [51:100] \\
  \beta_1(t) &= \cos(t\pi/20), x_1(t) = \cos(t\pi/20), \text{ if } t \in [151:200] \\
  \beta_1(t) &= 2.5, x_1(t) = \sin(t\pi/2), \text{ if } t \in [251:300] \\
  \beta_2(t) &= 0, x_2(t) = \epsilon_2(t), \text{ if } t \in [1:50], [101:150], [201:300] \\
  \beta_2(t) &= -\log(4t), x_2(t) = \cos(t + 10) + 0.01, \text{ if } t \in [51:100] \\
  \beta_2(t) &= 0.2\sqrt{t}, x_2(t) = -\sin(t\pi/50), \text{ if } t \in [151:200]
\end{align*}
\]

(6.7)

where \( \epsilon \) and \( \epsilon_i \) follow a normal distribution with mean 0 and variance 0.3. The generated data of \( y \) and \( x_i \) are shown in Fig. 6.2A. The FC between \( y \) and \( x_i \) are evaluated by s-FC and d-FC (included sliding-window analysis (window size = 20 time points, step = 1 time point), FLS (\( \mu = 20 \)), and KF with default parameters (Peng and Aston, 2011)); the s-FC and d-FC by sliding widow method is drawn as the pink and green line, respectively. The yellow filled area indicates the 95% confidence intervals for \( \beta \) coefficient (red line) estimated by KF method (Fig. 6.2 B and C), and there is no significant connectivity between the two signals at a time point when the enclosed range did not cover zero; the overlapped blue line is \( \beta \) estimated by FLS method. These results suggest that both the FLS and sliding window analysis could capture ground truth \( \beta \) over time. Under the different parameters, sliding window analysis and FLS may induce different results, experimental outcomes of FLS for \( \mu = 0.01, 0.1, 1, 10, 100, 1000, \) and 1000 are plotted in Fig. 6.3.

6.3.2 fMRI Data

We selected 32 young healthy subjects (10 females, all right-handed; age: 25.19±6.71 years) from our previous studies (Zhang et al., 2011; Liao et al., 2013b). The subjects had no history of neurological disorder or psychiatric illness and no gross abnormalities in the brain MRI images. Written informed consent was obtained from all subjects. The study was approved by the Local Medical Ethics Committee at Jinling Hospital, Nanjing University School of Medicine.

We performed functional neuroimaging acquisitions using a Siemens Trio 3T scanner at Jinling Hospital. We used foam padding to minimize head motion. We acquired resting-
DynamicBC

state functional images using a single-shot, gradient-recalled echo planar imaging sequence (250 volumes, repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, field of view = 240 × 240mm², inter-slice gap = 0.4 mm, voxel size = 3.75 × 3.75 × 4mm³, 30 transverse slices aligned along the anterio-posterior commissure). Subjects were instructed simply to rest with their eyes closed, not to think of anything in particular, and not to fall asleep. Subsequently, we acquired 3D T1-weighed anatomical images in sagittal orientation using a magnetization-prepared rapid gradient-echo sequence (repetition time = 2300ms, echo time = 2.98 ms, flip angle = 9°, field of view = 256 × 256mm², voxel size = 0.5 × 0.5 × 1mm³, 176 slices without inter-slice gap).

6.3.3 Preprocessing

Functional images were preprocessed using the REST (Song et al., 2011), DPARSF (www.restfmri.net) (Chao-Gan and Yu-Feng, 2010) and SPM8 (www.fil.ion.ucl.ac.uk/spm) toolkits. We excluded the first 10 images to ensure steady state longitudinal magnetization, and then we corrected the remaining images for temporal differences and head motion. No translation or rotation parameters in any given data set exceeded ±1mm or ±90°. The individual 3D T1-weighted anatomical image was coregistered to the functional images. The 3D T1-weighted anatomical images were segmented (grey matter, white matter, and cerebrospinal fluid). A nonlinear spatial deformation was then calculated from the grey matter images to a grey matter template in Montreal Neurological Institute (MNI) space using 12 parameters that were defined by affine linear transformation. This transformation was then applied to the functional images. The normalized images were re-sliced at a resolution of 3 × 3 × 3mm³. Nine sources of variances including six head motion parameters, averaged signals from cerebrospinal fluid and white matter, and global brain signal were regressed. Next, the data were band-pass filtered (0.01~0.08 Hz).

6.3.4 Seed-to-voxel based static and dynamic FC patterns

For seed-to-voxel analysis, a sphere (radius = 6mm) in the posterior cingulate cortex (PCC) (MNI coordinates: -2, -48, 28) was defined as the seed according to previous study (Spreng et al., 2013). The averaged BOLD time series was then obtained from the PCC and linear Pearson correlation analysis was performed in a voxel-wise way using full-length time series to generate static FC (s-FC) map. Next, the s-FC map of each subject was converted into z map by Fishers z transformation. Finally, z maps were combined across subjects using a fixed-effects analysis (sum and divided by the square root of number of subjects) to generation group s-FC map. The static FC pattern was consistent with previous resting-state fcMRI studies (Fig. 6.4A) (Fox et al., 2005; Fransson, 2005; Zhang et al., 2011). The PCC showed positive s-FC with medial prefrontal cortex (mPFC), bilateral inferior parietal lobule, middle temporal gyrus, and superior frontal gyrus. These
regions are considered part of the default mode network (DMN) (Raichle et al., 2001). In addition, the PCC showed negative s-FC with brain regions involving the fronto-parietal control network (FPCN), and the dorsal attention network (DAN).

The PCC seed above-mentioned was also applied to dynamic FC (d-FC) analysis. The FLS analysis strategy was selected for illustrating here. Dynamic FC organizations of one representative subject are shown in Fig. 6.4B (see corresponding movie 1 in Supplementary). To displaying PCC seeded FC dynamics, two target ROIs with 6 mm radius sphere (mPFC, MNI coordinates: [6, 51, 9], and superior parietal lobule (SPL), MNI coordinates: [63, -33, 39]) were identified in s-FC map (Fig. 6.4A). As seen from d-FC time series, FC between the PCC seed and the mPFC target, which both are belongs to the DMN, is relatively stable (solid red line); while FC between the PCC seed and SPL target involved in the DAN is highly non-stationary (solid blue line), in some cases exhibiting both strongly negative and correlations within the whole scan. These results give an evidence that the more variable FC between brain regions in distinct networks than within one network (Allen et al., 2014).

### 6.3.5 Seed-to-voxel based static and dynamic EC patterns

For static and dynamic EC analysis, we also defined the PCC as seed (see above). The averaged PCC BOLD time series was computed the GCA value of each voxel full-length time series, resulting in static EC (s-EC) map. Then, the s-EC map of each subject was combined across subjects using a fixed-effects analysis to generation group s-EC map. The s-EC from the PCC to whole brain (out map) and whole brain to PCC (in map) were illustrated in Fig. 6.5A.

Subsequently, we evaluated dynamic EC using the sliding-window GC analysis. We calculated GC maps between the PCC time series and all other brain voxel for a sliding-window of 50 volumes. For each sliding-window, we obtained the GC value in and out maps. The window was then shifted by 5 volumes and a new GC maps was calculated. This analysis strategy permitted to estimate dynamic EC over time. The dynamic EC map showing Granger causality from whole brain to the PCC (upper panel) and from the PCC to whole brain (bottom panel) are illustrated as in Fig. 6.5B (see Supplementary Movies 4 and 5). As see from d-EC time series of the target region mPFC, both the in-and out-influence are relatively stable and consistent changes across time.

### 6.3.6 ROI-to-ROI based static and dynamic FC networks

To illustrate the ROI-to-ROI based dynamic FC networks, we selected 43 ROIs, which are involved in the DMN, DAN and FPCN in line with the previous study (Spreng et al., 2013). Detailed brain regions and corresponding MNI coordinates and abbreviations of each ROI are shown in Table 6.1. We extracted the averaged BOLD time series from the
each ROI (6 mm radius sphere) from each subject. We computed the Pearson linear correlation coefficient between a pair of ROIs using the full length of the time series, and the square 43×43 s-FC matrix was obtained individually. Then, s-FC matrices after Fishers $z$ transformation were combined across subjects using a fixed-effects analysis to generate group s-FC matrix. To visualize the s-FC network, we positioned the regional centroid of each ROI (node) according to its MNI coordinates, and defined the threshold ($P<0.01$, Bonferroni corrected) to remove spurious connection (edge). Node strength was computed as the sum of the weights of all the connections of a given ROI. Finally, sFC network was visualized using the BrainNet Viewer (www.nitrc.org/projects/bnv/) (Xia et al., 2013) (Fig. 6.6A). We observed that a high degree of integration within each sub-network and anti-correlation between the DMN and the DAN and FPCN. The PCC and mPFC exhibited the high node strength, considering as core hubs. These findings consistent with the previous studies (Fox et al., 2005; Spreng et al., 2013).

For dynamic FC analysis, the FLS analysis strategy was also used. Dynamic FC network organizations of one representative subject are shown in Fig. 6.6B (see Supplementary Movie 4). As seen from d-FC network dynamics, the fundamental organization, that is integration within network and fractionation between networks, is relatively stable across time (Fig. 6.6B, upper panel). However, the hub with high regional weights changed hands several times (Fig. 6.6B, bottom panel), suggesting greater FC variability in the hub for the cognitive process switch. To examine the FC dynamics of core hub PCC, we selected three target ROIs. They are left posterior inferior parietal lobule (pIPL.L), right middle temporal motion complex (MT.R), and right dorsolateral prefrontal cortex (dIPFC.R) in the DMN, DAN, and FPCN, respectively. As seen from the d-FC time series, connectivity between the PCC and pIPL.L (solid red line) is less non-stationary; while that between the PCC and MT.R and between the PCC and dIPFC.R is relatively high non-stationary. This dynamicFC finding would suggest that some brain regions reveal dual-aligned properties (Spreng et al., 2013).

### 6.3.7 Voxel-to-voxel based FC network evolved with absence seizures

Quantification of disrupted dynamical connectome in diseased brain would better understand the evolution of disorder. In the current work, we aimed to observe the transition of whole brain connectome that account for absence seizure onset and offset. To this end, the voxel-to-voxel based dynamic FC network was constructed for a representative patient with absence epilepsy.

The patient underwent simultaneous EEG-fMRI session by an MR-compatible EEG recording system (Brain Products, Germany). During fMRI acquisition, EEG data was
continuously recorded through a 10/20 systems with 32 Ag/AgCl electrodes attached to the scalp with conductive cream. EEG electrodes were connected to a BrainAmp amplifier, with a sampling rate of 5 kHz. The EEG data was processed offline to filter out MR artifacts and remove ballistocardiogram artifacts (Brain Vision Analyzer 2.0, Germany). Onset and end time of epileptic discharges were marked and classified according to both spatial distribution and morphology. For more detail about the EEG dataset, see our previous studies (Liao et al., 2013a; Zhang et al., 2014b). The resting-state fMRI data was preprocessed in line with the healthy subject, except to re-sliced at a resolution of 6\times6\times6\text{mm}^3 to minimize storage and computational requirements. Voxel-to-voxel analysis computed the bivariate FC between every pair of voxels without using a priori seed/ROI. We used the FLS analysis strategy here. In this case, we obtained the functional connectivity strength (FCS) maps for each time points as shown in Fig. 6.7 (see Supplementary Movie 5). According to information from simultaneously collected EEG data, the FCS maps were separated into preictal (time before seizure onset), ictal, and postictal (time after seizure end) time periods (see (Liao et al., 2013a)). As previously suggested, the thalamus and PCC were involved in seizure initiation, maintenance, and termination during absence seizures. We selected these two core brain regions as the ROIs to tracking the FCS dynamics. As seen from d-FCS network dynamics, there is a higher FCS of the thalamus (THA) during the ictal period relative to the periods before and after seizures (blue line). Conversely, the PCC d-FCS time series are lower during the ictal period (red line). These findings suggest that the total connections of thalamus and the PCC relate to mechanisms of seizure generation and suspension of default mode of brain function is consistent with an inhibitory effect of seizures on the default mode of brain function, respectively.

### 6.4 Discussion

We have presented the DynamicBC, a new MATLAB toolbox for the analysis of dynamic brain connectome from multiple functional neuroimaging. In contrast to now available toolboxes, such as, GIFT (Allen et al., 2014), eConnectome (He et al., 2011), BSMART (Cui et al., 2008), Conn (Whitfield-Gabrieli and Nieto-Castanon, 2012), we now understand that the DynamicBC encompasses both dynamic functional and effective connectivity indexes. The aim of the toolbox is to develop a user-friendly GUI for accessibly, and to analyze more comfortably the dynamic brain connectome in which a task or stimulus responses and spontaneous brain activity are measured. To our knowledge, the voxel-level whole brain (GC density/strength) index is firstly available in this toolbox, which could be used to identify the hub of incoming and outgoing information transferring (Wu et al., 2013b).

Particularly, in the current work, we employ FLS algorithm for uncovering the time varying...
coefficients of a regression model. Comparing to sliding-window strategy in which the window length is hard to priori define to statistical validation (Hutchison et al., 2013), the FLS algorithm is a data-driven approach to assess rapidly connectivity changes. In addition, the well-known methodology Kalman filtering will be added to obtain a comparable result of the transient dynamics (Kang et al., 2011). Meanwhile, FLS and KF model based dynamic EC algorithms will provide new options to capture the dynamic connectomes. The present toolbox not only illuminate how much d-FC varies over a scan, but also provide whether the range of d-FC time series variability is significantly different between two populations or between particular regions. The formal group comparisons are challenge for dynamic brain connectome, due to the multi temporal-dimensional nature of the outputs (Hutchison et al., 2013). According to previous studies, we presented two ways for group analysis. The first sophisticated one, clustering method, collapse the temporal dimension of dynamic connectivity maps/matrices into several outputs or a single one (Liu and Duyn, 2013; Allen et al., 2014). Then, we could perform routine statistical tests between one or more conditions. The second simple one, the variance of the dynamic FC/EC time series (as a proxy of how ”stable” a connection is) was calculated automatically. This quantification of dynamic brain connectivity would lead to an improved understanding of the physiological processes of the intact brain or neuro-pathologic mechanism of the diseased brain.

Another issue related with the recovery of EC networks from BOLD fMRI signal is the possibly confounding effect of the hemodynamic response. In order to decouple the neuronal activity and the hemodynamic responses, we suggest applying a blind deconvolution procedure, based on the detection of pseudo-events, to the BOLD fMRI signal (Wu et al., 2013a). This blind deconvolution codes have been released and freely available at http://software.incf.org/software/blind-hrf-retrieval-and-deconvolution-for-resting-state-bold. There are some future directions for the toolbox. Only bivariate dynamic connectivity index are implemented. Firstly, the multivariate or blockwise connectivity measures (Wu et al., 2011) will be integrated in future releases of the tool. Secondly, implementation of point process event related non-stationary dynamics of spontaneous activity would be desirable (Tagliazucchi et al., 2012a; Wu et al., 2013a). Thirdly, combining the different EEG rhythms covary with fMRI connectivity over time (Tagliazucchi et al., 2012b; Chang et al., 2013) will be implemented in the future in the toolbox. Finally, we will add a visualization module for dynamic connectome movie.

6.5 Conclusion

The DynamicBC toolbox offers a user-friendly and integrated framework to tracking brain connectome by functional and effective connectivity. We provide two brain dynamic analysis strategies and three ways to set connections measures. The illustrative results
showed the dynamics of functional connectivity patterns or network in healthy brain and the whole brain connectome evolved with absence seizures. The current version is freely available at www.restfmri.net/forum/DynamicBC. Users would raise questions and give comments by email (dynamicbrainconn@gmail.com) and online forum (http://www.restfmri.net/forum/). We hope that this toolbox would make the dynamic brain connectome technique easier to develop, and the clinicians will be benefited from the contribution of the toolbox.
Table 6.1: Regions of Interest of the DMN, DAN, and FCN. (The abbreviations listed are those used in this article, which slightly differ from the original abbreviations by (Spreng et al., 2013). MNI, Montreal Neurological Institute.)

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Abbreviation</th>
<th>MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x   y   z</td>
</tr>
<tr>
<td><strong>Default mode network</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior medial prefrontal cortex</td>
<td>amPFC</td>
<td>-8  56  14</td>
</tr>
<tr>
<td>Anterior temporal lobe (left)</td>
<td>aTL.L</td>
<td>-52 -10 -20</td>
</tr>
<tr>
<td>Anterior temporal lobe (right)</td>
<td>aTL.R</td>
<td>52  -4  -16</td>
</tr>
<tr>
<td>Dorsal medial prefrontal cortex</td>
<td>dmPFC</td>
<td>-8  50  34</td>
</tr>
<tr>
<td>Hippocampal formation (left)</td>
<td>HF.L</td>
<td>-26  -8  -24</td>
</tr>
<tr>
<td>Hippocampal formation (right)</td>
<td>HF.R</td>
<td>24  -14  -22</td>
</tr>
<tr>
<td>Inferior frontal gyrus (left)</td>
<td>IFG.L</td>
<td>-42  26  -14</td>
</tr>
<tr>
<td>Inferior frontal gyrus (right)</td>
<td>IFG.R</td>
<td>50  32  -6</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>PCC</td>
<td>-2  -48  28</td>
</tr>
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<td>Posterior inferior parietal lobule (left)</td>
<td>piIPL.L</td>
<td>-50 -60  28</td>
</tr>
<tr>
<td>Posterior inferior parietal lobule (right)</td>
<td>piIPL.R</td>
<td>58  -60  28</td>
</tr>
<tr>
<td>Precuneus</td>
<td>PCUN</td>
<td>-2  -60  20</td>
</tr>
<tr>
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<td>SFG.L</td>
<td>-8   20  62</td>
</tr>
<tr>
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<td>STS.L</td>
<td>-60 -28  -4</td>
</tr>
<tr>
<td>Superior temporal sulcus (right)</td>
<td>STS.R</td>
<td>50  -36  4</td>
</tr>
<tr>
<td>Temporal parietal junction (left)</td>
<td>TPJ.L</td>
<td>-44 -52  22</td>
</tr>
<tr>
<td>Temporal parietal junction (right)</td>
<td>TPJ.R</td>
<td>44  -58  18</td>
</tr>
<tr>
<td>Ventral medial prefrontal cortex</td>
<td>vmPFC</td>
<td>-2  44 -12</td>
</tr>
<tr>
<td><strong>Attention network</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal eye fields (left)</td>
<td>FEF.L</td>
<td>-24  2  62</td>
</tr>
<tr>
<td>Frontal eye fields (right)</td>
<td>FEF.R</td>
<td>24  -2  56</td>
</tr>
<tr>
<td>Inferior precentral sulcus (left)</td>
<td>iPCS.L</td>
<td>-36  0  28</td>
</tr>
<tr>
<td>Inferior precentral sulcus (right)</td>
<td>iPCS.R</td>
<td>42  6  26</td>
</tr>
<tr>
<td>Middle temporal motion complex (left)</td>
<td>MT.L</td>
<td>-44 -66  0</td>
</tr>
<tr>
<td>Middle temporal motion complex (right)</td>
<td>MT.R</td>
<td>54 -54  -6</td>
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<td>Superior occipital gyrus (left)</td>
<td>SOG.L</td>
<td>-18 -66  50</td>
</tr>
<tr>
<td>Superior occipital gyrus (right)</td>
<td>SOG.R</td>
<td>26  -64  54</td>
</tr>
<tr>
<td>Superior parietal lobule (left)</td>
<td>SPL.L</td>
<td>-30 -48  52</td>
</tr>
<tr>
<td>Superior parietal lobule (right)</td>
<td>SPL.R</td>
<td>38  -46  54</td>
</tr>
<tr>
<td><strong>Frontoparietal control network</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal gyrus (right)</td>
<td>SFG.R</td>
<td>12   18  62</td>
</tr>
<tr>
<td>Anterior inferior parietal lobule (left)</td>
<td>aIPL.L</td>
<td>-54 -48  48</td>
</tr>
<tr>
<td>Anterior inferior parietal lobule (right)</td>
<td>aIPL.R</td>
<td>50  -44  46</td>
</tr>
<tr>
<td>Anterior insula (left)</td>
<td>aINS.L</td>
<td>-30  20  -2</td>
</tr>
<tr>
<td>Anterior insula (right)</td>
<td>aINS.R</td>
<td>32  20  -4</td>
</tr>
<tr>
<td>Dorsal anterior cingulate cortex</td>
<td>dACC</td>
<td>6   30  40</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex (left)</td>
<td>dlPFC.L</td>
<td>-38  32  30</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex (right)</td>
<td>dlPFC.R</td>
<td>44  42  26</td>
</tr>
<tr>
<td>Medial superior prefrontal cortex</td>
<td>msPFC</td>
<td>-2  20  50</td>
</tr>
<tr>
<td>Middle frontal gyrus BA 6 (left)</td>
<td>MFC(BA6).L</td>
<td>-28  14  58</td>
</tr>
<tr>
<td>Middle frontal gyrus BA 6 (right)</td>
<td>MFC(BA6).R</td>
<td>26  16  48</td>
</tr>
<tr>
<td>Middle frontal gyrus BA 9 (left)</td>
<td>MFC(BA9).L</td>
<td>-40  24  34</td>
</tr>
<tr>
<td>Middle frontal gyrus BA 9 (right)</td>
<td>MFC(BA9).R</td>
<td>44  26  42</td>
</tr>
<tr>
<td>Rostral lateral prefrontal cortex (left)</td>
<td>rlPFC.L</td>
<td>-32  58  2</td>
</tr>
<tr>
<td>Rostral lateral prefrontal cortex (right)</td>
<td>rlPFC.R</td>
<td>32  58  8</td>
</tr>
</tbody>
</table>
Figure 6.2: The simulated data and dynamic interactions. (A) Signals are generated according to equation 6.7. The blue, green, and red lines denote signals $x_1$, $x_2$ and $y$, respectively. They are normalized to a mean=0 and a variance=0.3. (B, C) The s-FC and d-FC by sliding-window analysis is drawn as the peach-puff and green line, respectively. The 95% confidence intervals for $\beta$ coefficient (red line) estimated by the KF method is shown as the yellow filled area, and the blue line indicated $\beta$ estimated by the FLS method.
Figure 6.3: The differential $\beta$ amplitudes as estimated by the FLS method with different penalty weights $\mu$, which increase by powers of ten: 0.01, 0.10, 1, 10, 100, 1000, 10000. The grey line indicates the ground truth $\beta$. 
Figure 6.4: Illustration of the seed-to-voxel wise static functional connectivity (s-FC) and dynamic functional connectivity (d-FC). (A) Group-averaged s-FC map following the linear Pearson’s correlation analysis using the full-length of the resting-state BOLD fMRI signal with a seed placed in the posterior cingulate cortex (PCC) (MNI coordinates: -2, -48, 28, 6mm radius sphere). (B) Dynamic FC map following FLS analysis with the PCC seed of a representative healthy subject. Two target ROIs with a 6 mm radius sphere were placed in the medial prefrontal cortex (mPFC, MNI coordinates: 6, 51, 9), and right superior parietal lobule (SPL, MNI coordinates: 63, -33, 39). The d-FC (solid line) and s-FC (dashed line) time series of mPFC (red line) and SPL (blue line) varied in a time-dependent manner. Warm and cool colors indicate brain regions with positive and negative temporal correlations with the PCC seed, respectively. Color scales represent the group-averaged correlation coefficient value (Z) of the s-FC map and individual β amplitude values of the d-FC map, respectively. See Supplementary Movie 1(http://online.liebertpub.com/doi/suppl/10.1089/brain.2014.0253/suppl_file/Supp_Movie1.gif).
Figure 6.5: Illustration for seed-to-voxel wise static effective connectivity (s-EC) and dynamic effective connectivity (d-EC). (A) Group-averaged s-EC map following linear residual-based Granger causality analysis (GCA) using full length of resting-state BOLD fMRI signal with a seed placed in the posterior cingulate cortex (PCC) (MNI coordinates: -2, -48, 28, 6mm radius sphere). (B) Dynamic EC map following sliding-window analysis of linear residual-based GCA with the PCC seed of a representative healthy subject. One target ROI with 6 mm radius sphere placed in the medial prefrontal cortex (mPFC, MNI coordinates: 3, 39, 18). The d-EC (solid line) and s-EC (dashed line) time series of mPFC from the in map (red line) and out map (blue line) vary across time. Warm and cool colors indicate brain regions with in influence (from whole brain to the seed) and out influence (from seed to whole brain), respectively. Color scales represent group-averaged GC value (F) of s-EC map and individual β amplitude values of d-EC map, respectively. See Supplementary Movies 2(http://online.liebertpub.com/doi/suppl/10.1089/brain.2014.0253/suppl_file/Supp_Movie2.gif) and 3(http://online.liebertpub.com/doi/suppl/10.1089/brain.2014.0253/suppl_file/Supp_Movie3.gif).
Figure 6.6: Illustration for ROI-to-ROI wise static functional connectivity (s-FC) and dynamic functional connectivity (d-FC). (A) Group-averaged pairwise correlation matrix (upper panel) following linear Pearson correlation analysis using full length of resting-state BOLD fMRI signals from 43 ROIs. This correlation matrix was visualized by brain network (bottom panel). (B) Dynamic functional correlation matrix (upper panel) and brain network (bottom panel) following FLS analysis among pairwise ROIs of a representative healthy subject. The d-FC (solid line) and s-FC (dashed line) time series between the PCC and other three ROIs vary across time. Abbreviations of ROI are indicated in the text. Warm and cool colors in correlation matrix indicate positive and negative correlations, respectively. See Supplementary Movie 4 (http://online.liebertpub.com/doi/suppl/10.1089/brain.2014.0253/suppl_file/Supp_Movie4.gif).

Figure 6.7: Dynamic functional connectivity strength (FCS). We calculated the dynamic FCS using FLS analysis strategy of pairwise voxels of a representative patient with absence epilepsy. The yellow shadow indicates ictal period marked by simultaneously collected EEG data. The d-FCS time series of the PCC (red line) and thalamus (THA) (blue line) vary preictal, ictal and postictal periods. See Supplementary Movie 5 (http://online.liebertpub.com/doi/suppl/10.1089/brain.2014.0253/suppl_file/Supp_Movie5.gif).
In this dissertation we explored the statistical methodology to track the resting state brain dynamics from fMRI data. This implies solving a typical high dimensionality and small-sample problem essentially. A full spatiotemporal model of the resting state fMRI data is generally not feasible and lots of shortcuts are taken as alternative approaches. They are all developed under the framework of functional segregation (activation) and integration (connectivity), which are the two fundamental aspects on brain function (Friston, 1994). This dissertation is organized following this framework.

7.1 Functional segregation

Functional segregation implies that a function can be localized in a cortical area. Lesions and electrical stimulation paradigms are the most employed method to test the specific function of a brain area (such as perceptual or motor processing). On the other hand fMRI is a non-invasive tool for studying brain function. The external task stimulus induced dominant activation in specific cortical area, while the functional activities in resting state widely spread on the whole brain. Yet, there are very few studies on the hemodynamic response to these spontaneous neural activity, most of them focus on the other BOLD profiles such as frequency characteristic of low frequency fluctuations (Fransson, 2005; Zang et al., 2007), which do not depict how the BOLD response to neural activity. This could be attributed to the absence of spontaneous activity information in task free paradigm, which results in GLM can not be directly applied. There are already some statistical approaches can recovery the event and onset from unknown activation profiles, such as change point analysis (CPA), total activation (TA). However some restrictions always apply to these methods: CPA is developed for task fMRI and it employs a multi-subject (mixed-effects)
extension of exponentially weighted moving average method for activation voxel screening (Lindquist et al., 2007; Robinson et al., 2010), which cannot be directly applied to resting state; TA makes use of a prior knowledge of the HRF, which is not suitable for HRF recovery (Karahanoglu et al., 2013). Inspired by evidence that cortical events which can be modeled as a point process drive the resting state BOLD signal (Tagliazucchi et al., 2012a), a blind HRF deconvolution procedure was developed in the GLM framework (Wu et al., 2013a), which involved both the HRF retrieval and deconvolution. Simulation and empirical resting state fMRI data have been used to validate the blind HRF deconvolution method. However, a comprehensive investigation of resting state HRF is still missing, which is the foundation of our blind HRF deconvolution algorithm. In addition, the simulation dataset tested in (Wu et al., 2013a) is designed for the pondering the connectivity algorithm performance in directional connectivity recovery, and only the ground truth connectivity structure is provided (Smith et al., 2011). We simulate the resting state BOLD via the Balloon model, in which the transit time is changed limited at a range of physiological condition (Chapter 2). The estimated HRFs essentially recovery the ground truth HRFs. To further verify the hypothesis that the recovered resting state HRF is an actual HRF and not some other characteristic of the BOLD signal, an Arterial Spin Labeling (ASL) dataset is employed to estimate the resting state CBF, which is the main component of resting state HRF. In this dataset, the BOLD and pCASL images are acquired separately for each subject. The baseline neural activities are assumed to be stable in both runs. The observed highly spatial correlation in CBF and HRF response height maps not only reflect the effectiveness of proposed HRF retrieval algorithm, but also confirm our hypothesis. As the pCASL and BOLD images are all collected from the MRI machine, some intrinsic noises may induce the similar imaging results. Again, we employ a simultaneous EEG-fMRI recording to seek for a electrophysiological evidences for our algorithm. Two alpha power correlated brain area show that higher correlation can be found after HRF deconvolution. In addition, the different HRF shape observed in these two areas points to the well-known phenomenon of alpha-power and BOLD signal correlation. These results from multimodal imaging reveal the neural mechanisms underlying the spontaneous point process induced HRF. Moreover, similar results are discovered from the modulation of HRF induced by propofol anesthesia and pathological vegetative state, which is consistent with the previous studies utilizing Positron Emission Topography (PET) (Chapter 3). This result supports the feasibility of the proposed blind HRF from tissue metabolic activity. In this dissertation, the canonical with delay and dispersion derivatives (canon2dd) and sFIR model are employed as HRF basis functions. They could reduce the bias in the linear estimation framework; however, as the noisier parametric estimation is accompanied by more flexible models, the explanation of results from these two models should consider the balance between flexibility to model HRF variations and power. In addition, as shown in HRF simulation tests, the accurate values of HRF parameters are valuable but less robust to highly noisy fMRI data: a
repeatable results under same SNR could be relevant for empirical fMRI studies.

### 7.2 Functional integration

The HRF depicts how a dynamic BOLD response follows an external or internal stimulus in a brain area; conversely, functional integration is used to describe how different brain areas interact. One challenge for this connectivity analysis is to bridge the gap between the high dimensionality of the variables and the statistical models of the whole brain. Statistical techniques such as averaging, independent component analysis (ICA) and principal component analysis (PCA) have the benefit of reducing the dimensionality of whole brain analysis. Besides, most of connectivity studies only explore priors or hypothetical brain circuits. Thus only a small number of highly constrained spatial regions can considered which in complex neurophysiological models such as Dynamical Causal Modeling (DCM). Nevertheless, with approaches such as DCM, only few nodes may involve a very large parameter space, resulting in a potential loss of accuracy. There is already a considerable number of connectivity studies including hemodynamic physiological process in their multivariate model; such studies however cannot always cope with high dimensional multivariate models (optimization approach, such as LASSO, may deal with it, but still cannot efficiently solve very high dimensional problems, even after dimensional reduction by ICA or PCA). Performing a HRF deconvolution before further connectivity analysis is a quick solution to this issue (Chapter 4). Meanwhile, statistical analysis of the joint probability of the occurrence of spontaneous point process events is enough to evaluate information transfer between two regions, which also reduce the data dimension (Chapter 4). This pairwise approach should nevertheless be extended to the multivariate case. Other statistical techniques such as partial conditioning could be subsequently used to reduce the dimensionality (Marinazzo et al., 2012). Undoubtedly, the most informative variables included in the multivariate model are the main factor that essentially affects model estimation. Synergy and redundancy in simultaneously recorded variables therefore affect the statistical inference on the brain dynamical connectome in a multivariate model, in the same way in which synergy and redundancy occur when information processing in the brain. We address this issue in Chapter 5. From the results reported regarding in the precuneus, not only the same subsystems (i.e. the Default Mode Network (DMN)), but other functional networks also contribute redundant information for the future state of this sink hub. Due to computational complexity, more appropriate or feasible algorithms should be developed to find high dimensional multiplets at voxel level. Additionally, quantifying changes in functional connectivity metrics over time may provide greater insight into fundamental properties of brain networks (Chapter 6). However, dynamic analysis is particularly sensitive to noise. The variations in the magnitude of noise levels across the scan, as well as non-neuronal events can be misinterpreted as dynamics of
FC. It is therefore critical to reduce all known non-neural contributions to the fMRI time series during pre-processing. Another challenge of interpreting apparent temporal variations in FC metrics is that the BOLD signal time series itself may be non-stationary. It is important to acknowledge these issues as the field proceeds to develop and interpret measurements of dynamic FC.

7.3 Future directions

GLM is an extremely rigid method, minor flaws in modeling can result in severe power loss. Examining the appropriateness of the GLM model in resting state fMRI is encouraged and valuable, but challenging due to the massive amount of data (Cassidy et al., 2012). Linear time invariance is assumed in our blind HRF retrieval algorithm: considering a time varying HRF could be more meaningful when tracking the dynamic brain activity under different physiological condition. Resting state and task related HRF comparison is being performed in our ongoing work, which could be helpful to further understand the BOLD-HRF mechanism. metabolic activity or CBF revealed by PET also is being explored to be compared with resting state HRF, which could strengthen the physiological validation of HRF retrieval from resting state recordings. It must also be considered that the fMRI BOLD signal predominantly shows only changes in deoxy-hemoglobin (HbR), which can make it difficult to disambiguate changes in total hemoglobin from changes in oxygenation. Investigation of this phenomenon by other techniques such as multi-spectral optical intrinsic signal imaging (MS-OISI, it can distinguish between changes in oxy-, deoxy- and total hemoglobin), near infrared reflectance spectroscopy (NIRS), could be meaningful and valuable to understand the basis of HRF. Meanwhile, the point process approach should be suitably modified for application and integration with these new modalities. Most functional connectivity approaches are less sensitive to HRF variability even in the absence of HRF in their model. This is not the case for effective connectivity, especially for lag based methods. As shown in a simulation study involving the nonlinear balloon model simulation, the accurate estimation of connection directionality is more difficult to achieve. Apart from the low sample rate (3 s in (Smith et al., 2011)), stimulus design, SNR and HRF variability also play an important role in directional connectivity recovery. In contrast to black-box in their simulation data (Smith et al., 2011), a comprehensive simulation studies including all possible disturbance factors could be crucial if we wanted to infer the statistical power of lag based methods. Furthermore, a test-retest study of how resting state HRF deconvolution affects brain connectivity obtained by lag based method should be performed for further validation of this approach in empirical fMRI data. Due to the high dimensionality in fMRI data, most of studies do not involve HRF variability in dynamic brain connectivity. A time varying state space model will likely be a convenient solution. Statistical analysis of dynamic connectivity matrices is necessary to
recovery useful information from these mount of plausible functional networks. We only include clustering and spectral algorithms in DynamicBC toolbox, further algorithms will be developed and added as a plug-in.
Peer-reviewed publications


- **Wu, Guo-Rong**, Wei Liao, Sebastiano Stramaglia, Ju-Rong Ding, Huafu Chen, and Daniele Marinazzo. 'A blind deconvolution approach to recover effective connectivity brain networks from resting state fMRI data.' Medical image analysis 17, no. 3 (2013): 365-374.

- **Wu, Guo-Rong**, Sebastiano Stramaglia, Huafu Chen, Wei Liao, and Daniele Marinazzo. 'Mapping the voxel-wise effective connectome in resting state FMRI.' PloS one 8, no. 9 (2013): e73670.


Conference contributions


- **Wu, Guorong**, Gopikrishna Deshpande, Steven Laureys, and Daniele Marinazzo. 'Retrieving the Hemodynamic Response Function in Resting State FMRI: Methodology and Application.' In 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2015.


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Het voornaamste doel van dit doctoraat is het verder methodologisch onderzoek naar neuronale netwerken door middel van het gebruik van functionele beeldvorming bij personen in rust (rust fMRI). Normaliter geeft een standaard rust fMRI veel ruis in de data samen met een complexe spatiotempeorele correlatie structuur. Deze thesis heeft twee belangrijke doelstellingen om zulke complexe data sets te analyseren. Ten eerste wordt het verband gelegd tussen de geobserveerde neuronale activiteit in de hersenen en het opgenomen signaal met de scanner. Ten tweede worden deze neuronale netwerken in kaart gebracht samen met uitvoerende functies in het brein. Deze bekomen kennis kan dan gebruikt worden voor om psychische, cognitieve en zelfs pathologische functies te evalueren. Elk van deze doelstellingen wordt hier verder onderzocht door het gebruik van verschillende statistische methoden: het gewone lineaire model (GLM), maar ook functionele en effectieve connectiviteit analyses. GLM is een eenvoudige en efficiënte manier om fMRI data te analyseren, maar deze methode vereist een exacte tijdopname van start en duur van neuronale activiteit. Zonder simultane elektrofysiologische metingen zijn deze gegevens met rust fMRI moeilijk te interpreteren. Functionele connectiviteit betreft de statistische verbanden tussen de verschillende neuronal betrokken structuren. Effectieve connectiviteit (EC) is een relatief nieuw concept en het refereert naar directe of indirecte dynamische invloeden dat een welbepaald neuronaal netwerk uitoefent over een ander. Betreffende de EC zijn er reeds verschillende gevalideerde methoden in gebruik: de directe transfer functie, de partieel directe coherentie, en de transfer entropie. Maar ook Granger causaliteit, en dynamische causale verbanden worden gebruikt. Al deze methoden geven een eerder complementair inzicht in structuur en functie van het brein; de meesten ervan gaan er van uit dat de vorm van de hemodynamische respons functie (HRF) constant blijft over alle voxels in het brein en dit bij alle individuen. Nochtans kan deze aanpak significante fouten
genereren gezien de HRF vorm niet enkel kan verschillen tussen hersenstructuren maar ook tussen personen. Buiten deze moeilijkheden met de HRF interpretatie, is een ander belangrijke factor die aanleiding kan geven tot foute interpretaties met betrekking tot connectiviteit de introductie van overbodige variabelen. Limiterende factoren zijn het groot aantal verschillende variabelen waarmee rekening moet gehouden worden (dimensionaliteit) en het kleine aantal gebruikte subjecten. Bovendien leidt een bivariante analyse aanpak vaak tot vals positieve resultaten, een multivariante aanpak geeft mogelijk berekeningsproblemen door teveel of overbodige variabelen in het model te plaatsen.

Door de point process theorie en informatie theorie te gebruiken bekijken we in deze thesis in het bijzonder HRF variabiliteit en overbodige variabelen met betrekking tot connectiviteit. Hierbij worden alle individuele fMRI voxels geanalyseerd en hieruit worden de wordt de initiale neuronale activiteit gextraherd. De HRF wordt bepaald met GLM en wordt de HRF vorm verder statistisch verwerkt, gevalideerd en gebruikt in specifieke datasets. Vervolgens wordt een HRF deconvolutie uitgevoerd over het BOLD signaal om het intrinsieke neuronale signaal te capteren waarna het connectiviteitsnetwerk wordt opgebouwd en geanalyseerd op het gedeconvuleerde BOLD signaal. Het resulterende connectiviteitsnetwerk wordt verder grondig gevalideerd door gebruik te maken van ad hoc datasets.