



## Thresholding functional connectomes by means of mixture modeling

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### ABSTRACT

Functional connectivity has been shown to be a very promising tool for studying the large-scale functional architecture of the human brain. In network research in fMRI, functional connectivity is considered as a set of pair-wise interactions between the nodes of the network. These interactions are typically operationalized through the full or partial correlation between all pairs of regional time series. Estimating the structure of the latent underlying functional connectome from the set of pair-wise partial correlations remains an open research problem though. Typically, this thresholding problem is approached by proportional thresholding, or by means of parametric or non-parametric permutation testing across a cohort of subjects at each possible connection. As an alternative, we propose a data-driven thresholding approach for network matrices on the basis of mixture modeling. This approach allows for creating subject-specific sparse connectomes by modeling the full set of partial correlations as a mixture of low correlation values associated with weak or unreliable edges in the connectome and a sparse set of reliable connections. Consequently, we propose to use alternative thresholding strategy based on the model fit using pseudo-False Discovery Rates derived on the basis of the empirical null estimated as part of the mixture distribution.

We evaluate the method on synthetic benchmark fMRI datasets where the underlying network structure is known, and demonstrate that it gives improved performance with respect to the alternative methods for thresholding connectomes, given the canonical thresholding levels. We also demonstrate that mixture modeling gives highly reproducible results when applied to the functional connectomes of the visual system derived from the n-back Working Memory task in the Human Connectome Project. The sparse connectomes obtained from mixture modeling are further discussed in the light of the previous knowledge of the functional architecture of the visual system in humans. We also demonstrate that with use of our method, we are able to extract similar information on the group level as can be achieved with permutation testing even though these two methods are not equivalent. We demonstrate that with both of these methods, we obtain functional decoupling between the two hemispheres in the higher order areas of the visual cortex during visual stimulation as compared to the resting state, which is in line with previous studies suggesting lateralization in the visual processing. However, as opposed to permutation testing, our approach does not require inference at the cohort level and can be used for creating sparse connectomes at the level of a single subject.

### Introduction

Functional connectivity (FC) characterizes temporal correlations between signals in the nodes or regions-of-interest (ROIs) in the neuronal network. In functional Magnetic Resonance Imaging (Smith et al., 2013)

(fMRI), this concept is used in many contexts. FC serves to study the (co) activity in the neuronal networks, and to investigate links between activity in neuronal networks and cognitive abilities (Smith et al., 2015; Finn et al., 2015; Tavor et al., 2016; Smith, 2016; Chauvin et al., 2017) or clinical-behavioural covariates (Lynall et al., 2010; Garrity et al., 2007;

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Greicius et al., 2007; Soriano-Mas et al., 2009; Rausch et al., 2016; Oldehinkel et al., 2016; Mulders et al., 2015). It is also used to gain insights into hierarchical structures in the brain in rest and cognition (Smith et al., 2015; Bola and Borchardt, 2016), e.g., the hierarchical structure of sensory systems (Arcaro et al., 2015; Merhar et al., 2016).

In fMRI research, functional connectivity is typically operationalized by means of partial correlation (Marrelec et al., 2006). Since any two processes - even in the absence of underlying direct connection - will almost surely retrieve a non-zero partial correlation by chance, the partial correlation matrices should be constrained in order to remove unreliable connections<sup>2</sup>. As indicated in recent studies by van den Heuvel et al. (van den Heuvel et al., 2017), Zalesky et al. (2016), and Ginestet et al. (2011), the choice of thresholding method can influence the amount of weak connections present in the connectomes, which, in turn, yields an effect on the structure and global properties of the sparsified networks. For this reason, the choice of thresholding method can highly influence the results and interpretation of the results in a functional connectivity study.

There are a few leading approaches to the problem of sparsifying functional connectomes in the field.

Firstly, a popular approach to sparsifying functional connectomes is *proportional* thresholding (Achard and Bullmore, 2007; Bassett and Bullmore, 2009; van den Heuvel et al., 2008). In this thresholding scheme, a top percentage of all partial correlation values in a subject-specific functional connectome is selected. The main aim of this approach is to keep the number of connections fixed for all the individuals in order to eliminate the impact of network density on the comparison of graph metrics across groups. This method for sparsifying functional connectomes is currently the most popular approach in the field, which might be due to its simplicity.

Secondly, partial correlation matrix can be estimated with use of regularizers (Bishop, 2006). Regularization techniques impose sparsity on the network by using a loss function that penalizes for the number of non-zero entries in the connectivity matrix so that the weak connections are shrunk to zero. The shrinkage approach is used to drive weak connections to zero and then to accept everything that has not been set to zero as truly existing. Originally, the goal of the regularizing techniques was not thresholding connectomes, however this became one of the practical applications.

Lastly, thresholding can be performed on the basis of connection-specific significance levels obtained from permutation testing (Welch, 1990). Each of the functional connection can then be thresholded at edge-specific threshold level, according to the edge-specific null. Technically, computing significance levels through permutation testing can be done both at the population- or at the single subject level. On the single subject level, thresholds are estimated from the null-distribution of connections generated by breaking correlations between time series. On the other hand, in order to create the null distribution at the population level, region-specific time series are permuted between subjects, and partial correlation is computed for a number of surrogate networks obtained from permutations across subjects. However, in datasets in which signals are autocorrelated - such as fMRI data where the slow haemodynamic induces autocorrelations in the signal - building the null by shuffling the labels between subjects is preferred over permuting samples on the single subject level, as it keeps the autocorrelations intact.<sup>3</sup> For this reason, the population level approach was also used in the seminal paper by Smith et al. (2011). As a result, in practice, building significance intervals in permutation testing is only possible on the population (and not on the single subject) level in fMRI connectivity research.

<sup>2</sup> Neurobiologically speaking, one may argue that the brain is highly integrative and therefore, the connections represented by low values of a partial correlation should arguably be referred to as *weak* - in the sense of indistinguishable from the noise.

<sup>3</sup> We also demonstrate the effect of breaking autocorrelations on the results of permutation testing in [Supplementary Material 5](#).

In this work, we propose an alternative to the aforementioned methods: thresholding subject-specific connectomes by means of mixture modeling. To our knowledge, only one work has previously applied this method to model sparse resting-state functional connections (Tyszka et al., 2014). Here we provide a thorough investigation of this technique. Mixture modeling differs from permutation testing as the (pseudo)-null is built subject-wise across all possible connections in the connectome, as opposed to estimating connection-wise null distributions via permutation testing. The underlying assumptions here are that (i) the evidence for a non-zero connection are unrelated to the spatial location of the nodes, (ii) that non-zero connections are sparse and that (iii) there is a sufficient number of nodes so that the set of values for non-existing edges in the network can be used to estimate the within-subject null distribution of non-existing connections.

In our approach, mixture modeling is used in order to separate strong connections in the connectome from a pseudo-null, which is a mixture of noise with weak functional connections. We talk about the pseudo-null as in fact, the functional connectomes in the brain most likely have a scale-free distribution rather than being sparse (Eguiluz et al., 2005; van den Heuvel et al., 2008). Therefore, we can only talk about a 'pseudo-null' which consists of the 'true null' distribution of functionally disconnected pairs of nodes, and in addition to that, a part of the scale-free distribution which involve connections too weak to be discerned from the noise with any statistical inference methods. As mainly the strong connections are of interest in connectivity studies, this model choice is a justifiable simplification.

Mixture modeling is a valuable alternative as, on the contrary to permutation testing, it allows for creating connectomes both at the single subject- and at the group level. Furthermore, mixture modeling solves the problem relating to subject-specific proportional thresholding as a technique that allows for weak connections to pass the thresholding in some subjects (for instance, in subjects whose individual connectomes have low number of strong connections compared to other subjects) - which, in turn, changes the global properties in the networks. In mixture modeling, this is not the case, as the total number of connections in the sparsified network is not fixed per subject: *strong* and *weak* connections are determined on the basis of the subject-specific distribution of connections, and mixture modeling provides with a natural separation into the two classes.

The mixture modeling approach used here is popular in other contexts in fMRI research, especially as the basis for thresholding Independent Component Analysis-derived maps (Beckmann and Smith, 2004; Beckmann et al., 2005). It is also used in other applications such as GWAS studies in polygenic disorders (Thompson et al., 2015), where a mixture model is fitted to the distributions of effect sizes for all SNPs.

In our study, we validate mixture-model-based thresholding on the benchmark synthetic fMRI datasets (Smith et al., 2011) derived from Dynamic Causal Modeling generative model (Friston et al., 2003; Smith et al., 2011). Furthermore, we apply our thresholding approach to experimental fMRI datasets from the Human Connectome Project (HCP (Essen et al., 2013),) by creating a sparse connectome of the human visual system at rest and under visual stimulation (Barch et al., 2013). We chose the human visual system because this network incorporates one of best known functional architectures in the human brain, and this allows for qualitative comparison between the methods. We used the n-back working memory (WM) task data from the Human Connectome Project (Barch et al., 2013), because this task involves ongoing visual stimulation by presenting objects in the visual field of the participants. Since during the task, objects of a few categories were presented to the subjects, our hypotheses concentrated on connectivity of the areas responsible for object recognition such as the two areas of the lateral occipital cortex: LO1 and LO2 (Silson et al., 2013; Amedi et al., 2001; James et al., 2002). Multiple studies have revealed that these areas respond to objects defined by luminance, texture or motion but not when subjects view only backgrounds of different textures or coherently moving dots (Grill-Spector et al., 1998). Furthermore, object recognition in the visual system is known as a lateralized process (Warrington and Taylor, 1978): the right

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